



Alkaloid syntheis via novel azabicycles.

BOYNTON, Carole M.

Available from the Sheffield Hallam University Research Archive (SHURA) at:

<http://shura.shu.ac.uk/19384/>

A Sheffield Hallam University thesis

This thesis is protected by copyright which belongs to the author.

The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the author.

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given.

Please visit <http://shura.shu.ac.uk/19384/> and <http://shura.shu.ac.uk/information.html> for further details about copyright and re-use permissions.

POLYTECHNIC LIBRARY
POND STREET
SHEFFIELD S1 1WB

6704

100225471 X



Sheffield City Polytechnic Library

REFERENCE ONLY

ProQuest Number: 10694265

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



ProQuest 10694265

Published by ProQuest LLC (2017). Copyright of the Dissertation is held by the Author.

All rights reserved.

This work is protected against unauthorized copying under Title 17, United States Code
Microform Edition © ProQuest LLC.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

ALKALOID SYNTHESIS VIA NOVEL AZABICYCLES

BY

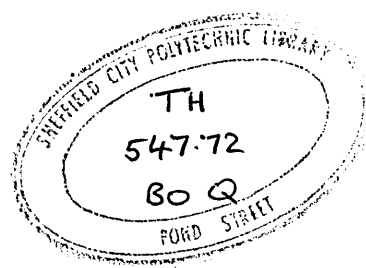
CAROLE M BOYNTON BSc CChem MRSC

A THESIS SUBMITTED TO THE COUNCIL FOR NATIONAL ACADEMIC AWARDS IN
PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF
PHILOSOPHY

SPONSORING ESTABLISHMENT : SHEFFIELD CITY POLYTECHNIC

COLLABORATING ESTABLISHMENT: GLAXO GROUP RESEARCH (WARE) LTD

SEPTEMBER 1988



C O N T E N T S

	<u>Page no</u>
Acknowledgements	1
Abstract	2
Conventions	3
1. Introduction to Pyrrolizidine and Indolizidine Alkaloids	4
2. Cycloalkene Synthesis by Intramolecular Wittig Reactions	43
3. The use of 5-acetylpyrrolidin-2-one in the synthesis of heterocyclic systems	71
4. The use of succinimide in the synthesis of heterocyclic systems	115
5. Experimental Section	132
References	183
Research Study Programme	192

ACKNOWLEDGEMENTS

I would like to extend my sincere gratitude to Dr. Alan Hewson for taking me on as a student and for his support, guidance and amazing display of patience.

I would also like to thank the Science and Engineering Research Council for the funding of this project and Dr. Alan Wadsworth from Glaxo for his co-supervision.

I am very grateful to Andrea Pedley for typing the manuscript and for her assistance in producing this thesis.

Finally, I would like to express sincere thanks to all staff and research students at Sheffield who have shown an interest and given help during my research.

Abstract

A basic introduction to pyrrolizidine and indolizidine alkaloids has been described along with a selection of recent syntheses of the said compounds.

Cycloalkene synthesis by intramolecular Wittig reaction has been reviewed and we describe the utility of this strategy in the formation of nitrogen-bridgehead bicycles which can then be used in alkaloid synthesis. Our initial studies on the viability of this strategy in the synthesis of fused pyrrolidone systems employed a Wittig reaction between 5-acetylpyrrolidin-2-one and vinylphosphonium salts. A comparison was made between three different vinylphosphonium salts but in each case the bicycle formed was present as a mixture with the Wittig by-product triphenylphosphine oxide. Various solutions to this problem were investigated including modification of the bicycle and also the formation of a water soluble vinylphosphonium salt. The difficulties encountered led us to the use of a vinylphosphine oxide which resulted in the formation of 5,6,7,7a - tetrahydro-1-methyl-2-phenylthio-3H-pyrrolizin-5-one in good yields. Desulphurisation gave 5,6,7,7a - tetrahydro-1-methyl-3H-pyrrolizin-5-one which has previously been converted into (±) - supinidine. Thus our method constitutes a formal total synthesis of (±) - supinidine.

Attempts at the preparation of analogues of 5-acetylpyrrolidin-2-one were unsuccessful but were in their preliminary stages at the close of the work.

Reaction of 5-acetylpyrrolidin-2-one with cyclopropylphosphonium salts were attempted without success but it is felt that the use of cyclopropylphosphine oxides would solve this problem.

Attempts at performing an intramolecular Wittig reaction on the imide carbonyl of succinimide using both cyclopropylphosphonium salts and butadienylphosphonium salts were unsuccessful but our investigations gave an insight into the cause of the failure - forcing conditions need to be employed to effect the cyclisation.

C O N V E N T I O N S

A broken line ----- denotes an α -configuration.

A solid tapered line \triangleleft denotes a β -configuration.

A wavy line \sim denotes either an unknown or unspecified configuration.

CHAPTER 1

An introduction to Pyrrolizidine and Indolizidine Alkaloids

1.1. Pyrrolizidine Alkaloids

1.1.1. Background

1.1.2. Occurrence and uses

1.1.3. Conformation of the pyrrolizidine nucleus

1.1.4. Biosynthesis of naturally occurring pyrrolizidines

1.1.5. Current pyrrolizidine synthesis

1.2. Indolizidine Alkaloids

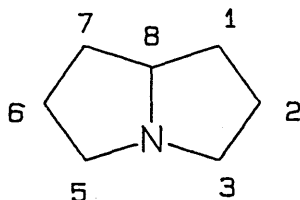
1.2.1. Background

1.2.2. Elaeocarpus Alkaloids

1.2.3. Dendrobatid Alkaloids

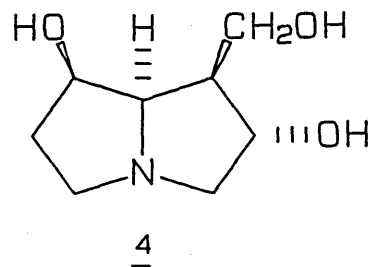
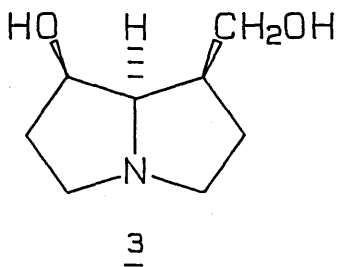
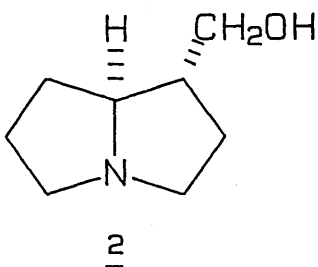
1.1.1. Background

The pyrrolizidine alkaloids are a large class of natural products which have attracted the attention of synthetic organic chemists for several decades.¹ These alkaloids have a broad distribution within the plant and animal kingdom and exhibit an incredible range of biological activity,² including antitumor, hypotensive, local anaesthetic, anti-spasmodic, anti-inflammatory, carcinogenic and especially hepatotoxic action. This alkaloid class possesses the 1-azabicyclo [3.3.0.] octane skeleton (1).



1

The alkaloids are usually composed of two moieties - a pyrrolizidine alcohol (which is called a necine), and a carboxylic, usually hydroxy acid (known as a necic acid) which are combined by an ester linkage. The pyrrolizidine moieties may appear as monohydric (as in trachelanthamidine 2), dihydric (as in platynecine 3) or trihydric alcohols (as in rosmarinecine 4).



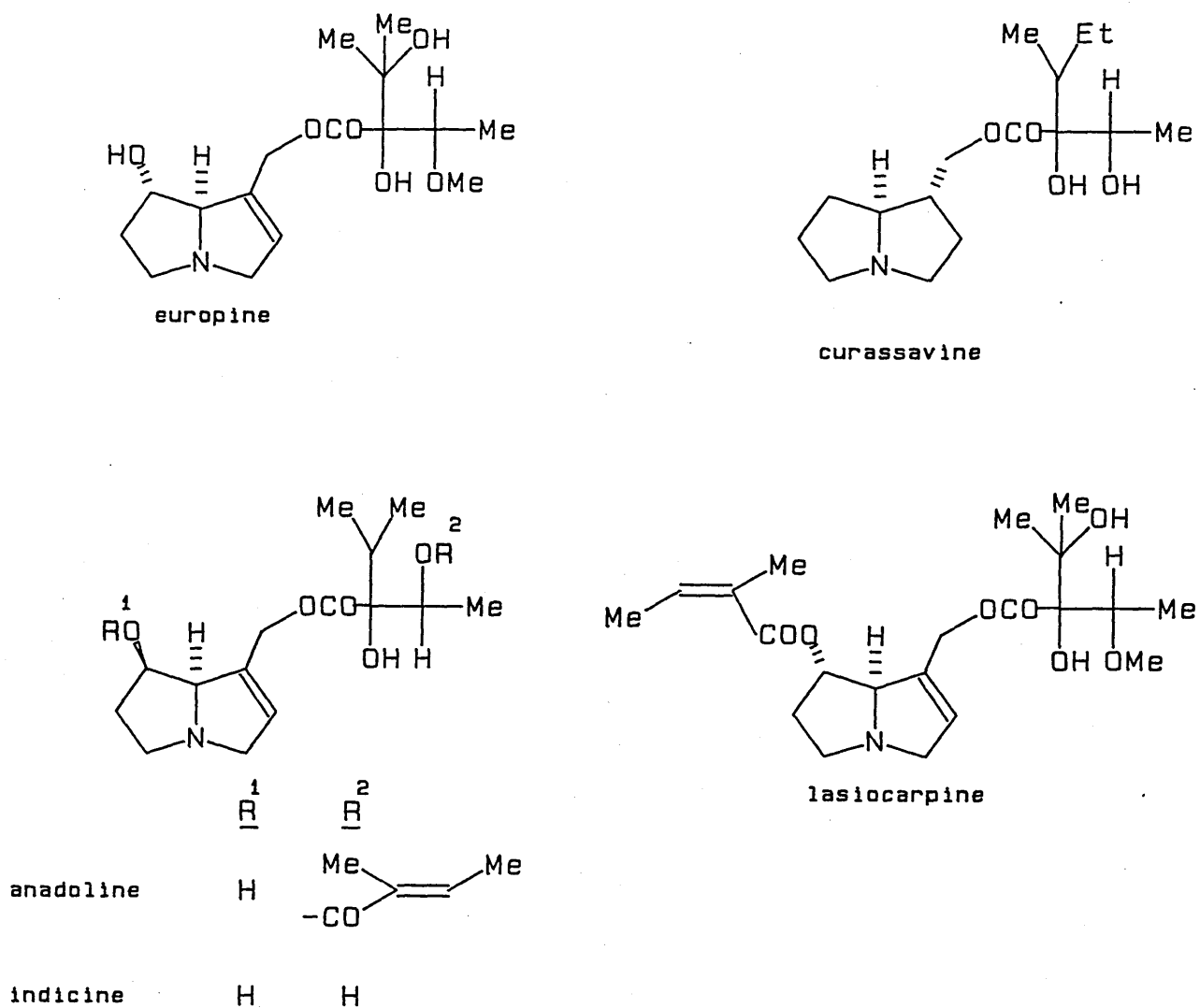


Figure 1

1 - methylenepyrrolizidine (7) and related compounds occur in plants in the free state, forming the special group of so-called "non-ester" pyrrolizidine alkaloids.⁵ (Figure 2).

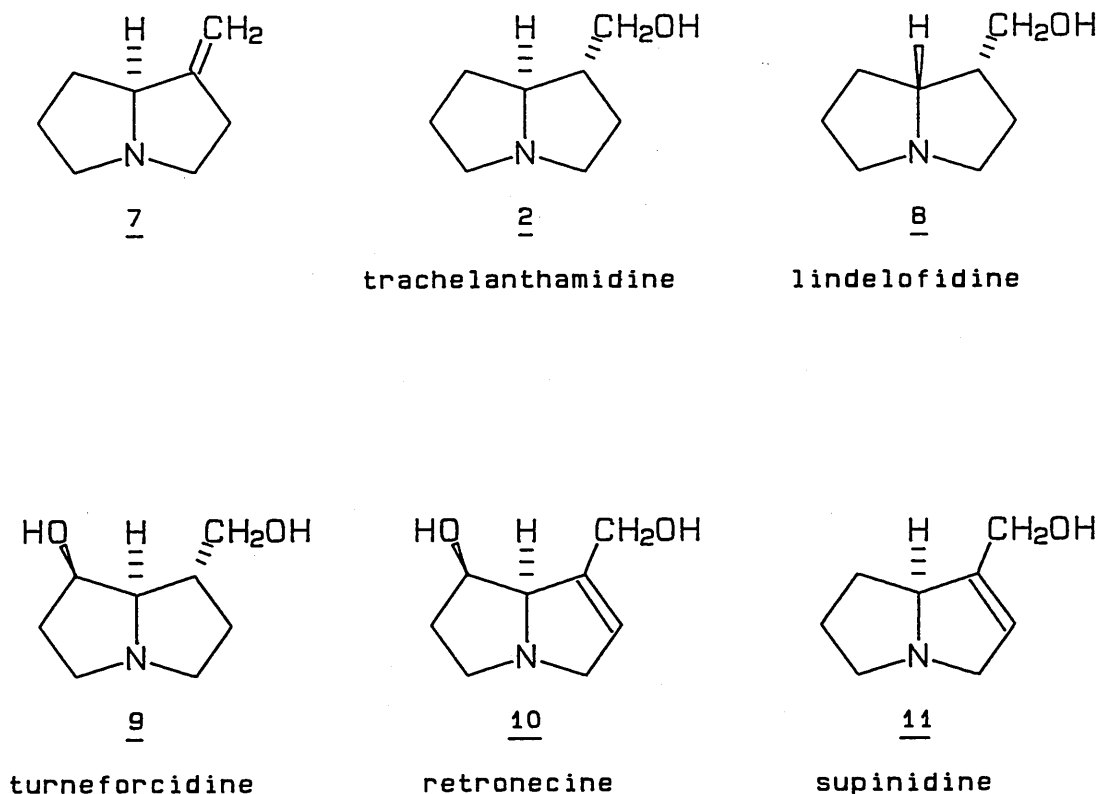
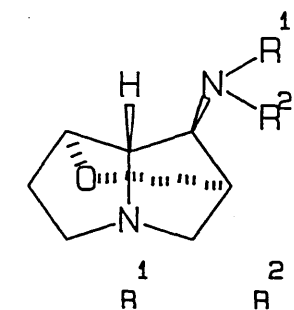


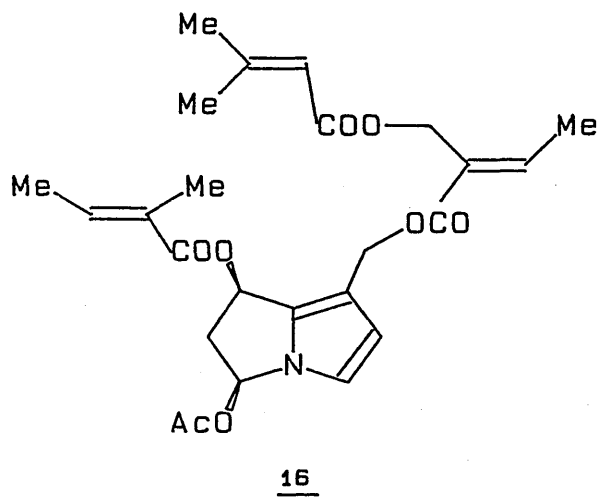
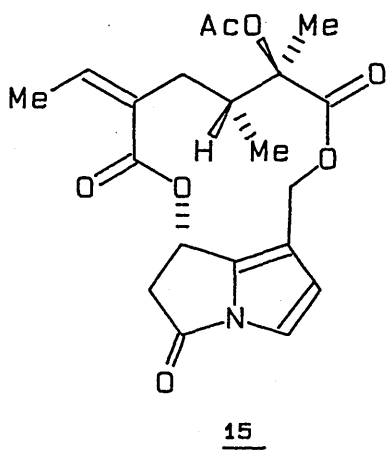
Figure 2 Non-ester pyrrolizidine alkaloids

A group of saturated amino pyrrolizidines loline (12), norloline (13) and lolinine (14) occurs in some grasses (family Graminae). These are not hepatotoxic, but they may play a part in other toxic actions of these plants.⁵ An association has recently been demonstrated between the presence of these pyrrolizidine alkaloids and an endophytic fungus infection in some plants. This raises the possibility, as yet unconfirmed, that loline alkaloids might be phytoalexins produced only in plants stressed by such infections.



<u>12</u>	H	Me
<u>13</u>	H	H
<u>14</u>	Ac	Me

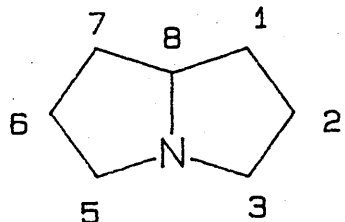
A number of pyrrolizidine alkaloids contain a dihydropyrrolizine nucleus.⁵ These include the dihydropyrrolizine senaetnine (15) and related esters, and acetoxy derivatives, for example, senampeline A (16). These alkaloids have not yet been tested for hepatotoxicity.



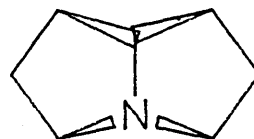
Pyrrolizidine alkaloids have been found to be present in several genera of the plant families of Compositae, Leguminosae and Boraginaceae etc.^{2(a)} They may grow in temperate climates, but some may require tropical or subtropical climates. Most of them are spring or summer annuals, but some may be biennial or perennial. They are mainly herbaceous species with a few shrubs and climbers and a small number of trees. There can be few areas in the world where grazing animals are not exposed to one or more pyrrolizidine containing species. Heavy losses of livestock due to the consumption of these plants have occurred over the years. The disease produced is characteristically chronic in nature, it is progressive and death commonly occurs weeks or months after consumption of the poison plant has ceased. Some pyrrolizidine derivatives, however, have found wide and varied use:⁶

Pyrrolizidine (1) and simple alkylpyrrolizidines are used as catalysts for the preparation of polymers and resins, particularly polyurethanes. They have been utilized also as lubricating oil additives and as hardeners for epoxyresins. Some of the quaternary pyrrolizidine salts are powerful parasiticides. A number of the naturally occurring alkaloids are hepatotoxic and carcinogenic but some derivatives have potentially useful physiological properties, including anaesthetic and antiviral activities, and a wide range of pharmaceuticals including anti-inflammatory drugs, have been prepared.

It is well known that the trans bicyclo [3.3.0.] octane is a rigid and strained system,⁷ whereas the cis isomer is almost strain-free. Pyrrolizidine (1) differs in that one of the carbon atoms is substituted by a trivalent nitrogen atom which does not rigidly fix the bicyclic system. For this reason pyrrolizidine (1) although it probably occurs in the preferred cis-conformation has no stereoisomers. The two rings of the pyrrolizidine system form a dihedral angle with the axis along the C8-N bond (17).

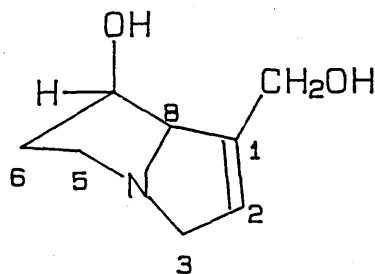


1

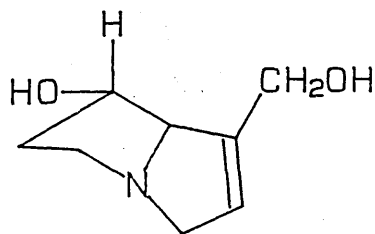


17

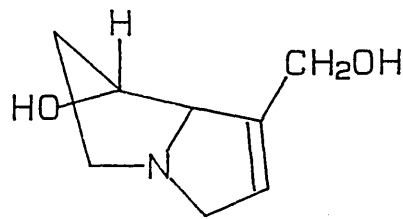
Culvenor and co-workers⁸ have concluded that retronecine would exist preferentially in an exo-buckled form (18) whereas heliotridine (19) is a mixture of rapidly interconverting exo- and endo-buckled forms.



18



19 exo



19 endo

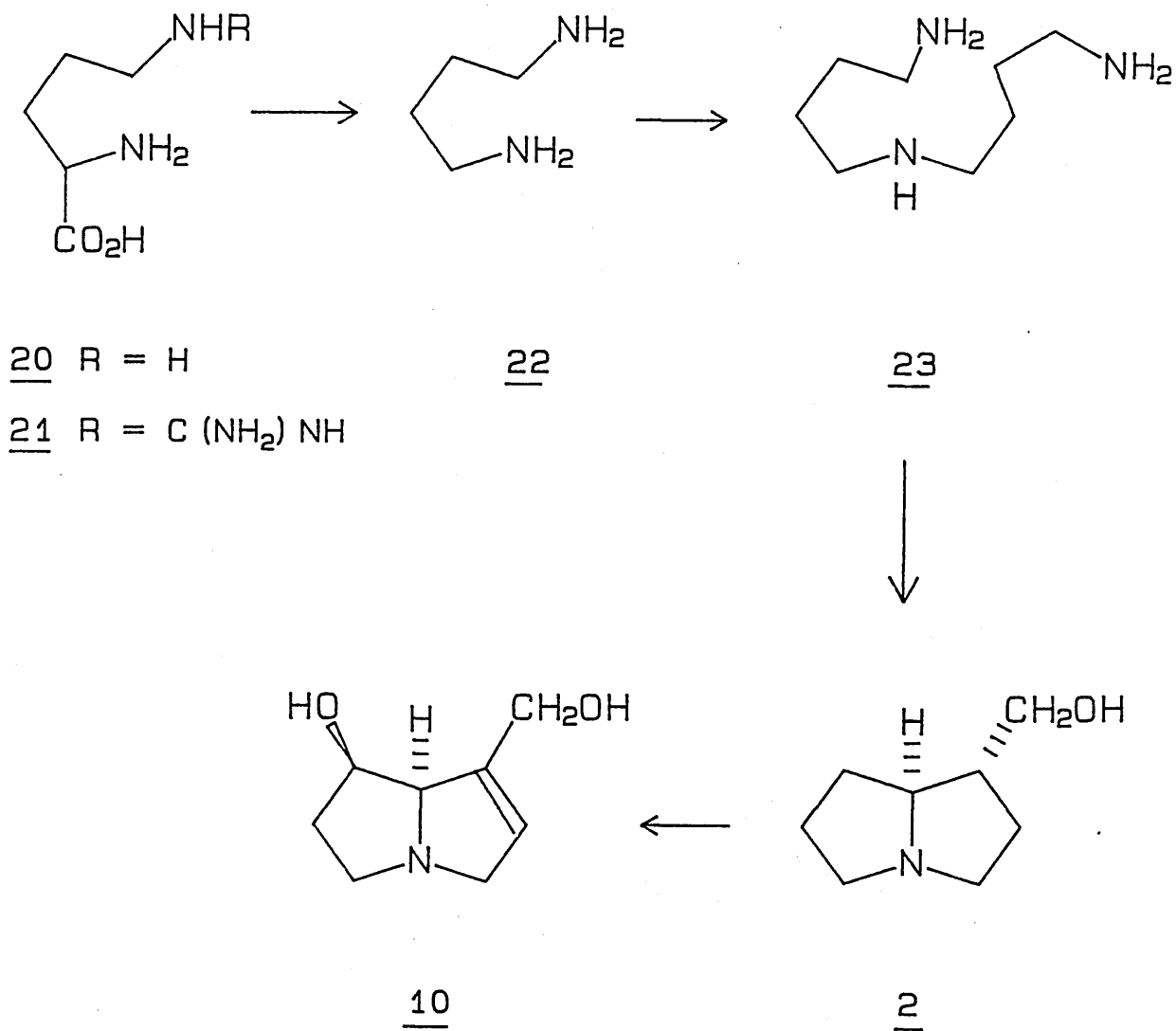
pyrrolizidine nucleus are:

- (a) strong puckering of the saturated 5-membered ring induced by torsional strain and non-bonded interactions;
- (b) near-planarity of the unsaturated 5-membered ring;
- (c) the improbability of inversion of the nitrogen atom because of the considerable energy difference (6 kcal/mol)⁸ between cis- and trans-fused 5-membered rings.

1.1.4. Biosynthesis of Naturally Occurring Pyrrolizidines

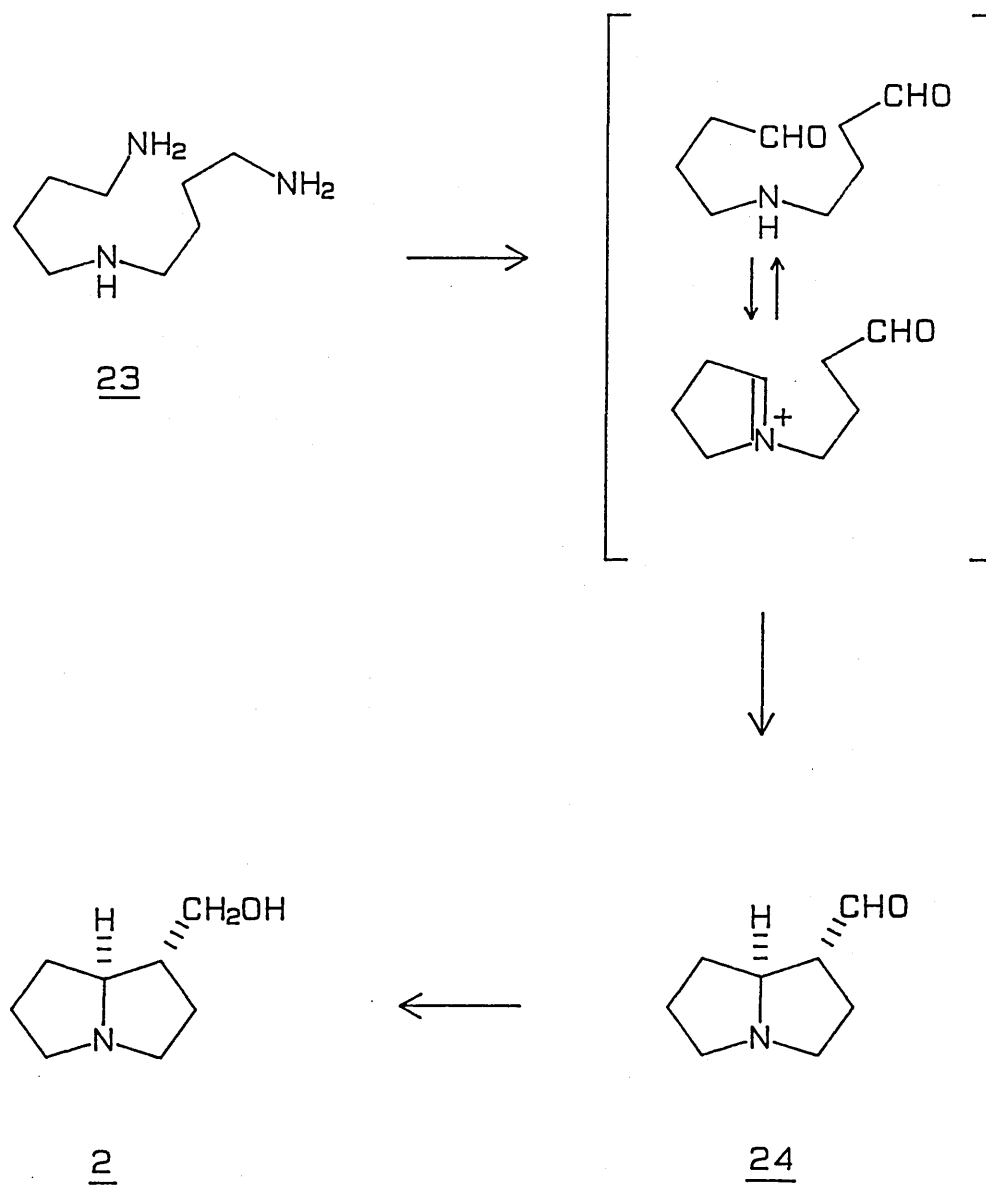
Robinson's original suggestion⁹ that the natural pyrrolizidine bases are derived in vivo from two molecules of ornithine has been supported by studies using ¹⁴C-labelled compounds¹⁰.

Retronecine (10) is the most commonly encountered pyrrolizidine base^{1(a)} and as such is the only necine base whose biosynthesis has been studied in detail. To summarise a great deal of work, it has been established that retronecine is derived biosynthetically from L-ornithine(20) or L-arginine(21) (but not from the D-isomers) via putrescine (22)¹¹ (Scheme 1).



SCHEME 1

Two molecules of putrescine (22) combine to form homospermidine (23). The pyrrolizidine ring is believed to be formed by a Mannich type cyclisation after oxidation of the primary amino groups in homospermidine (23) to the corresponding dialdehyde¹². Reduction of the 1-formylpyrrolizidine (24) leads to the next intermediate which has been established in the biosynthetic pathway, trachelanthamidine (2) (Scheme 2).



SCHEME 2

The biological synthesis of trachelanthamidine (2) has been simulated in vitro¹² supporting the theory that homospermidine is a key intermediate in retronecine biosynthesis.

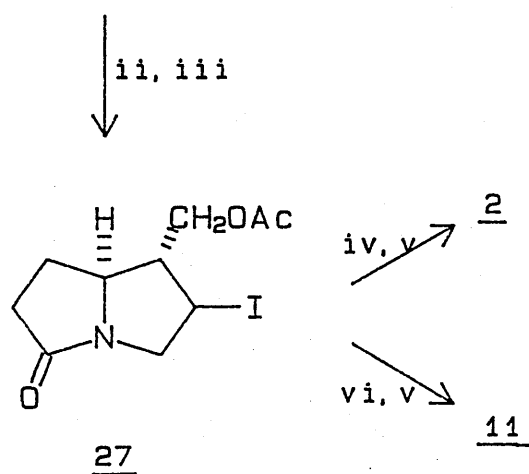
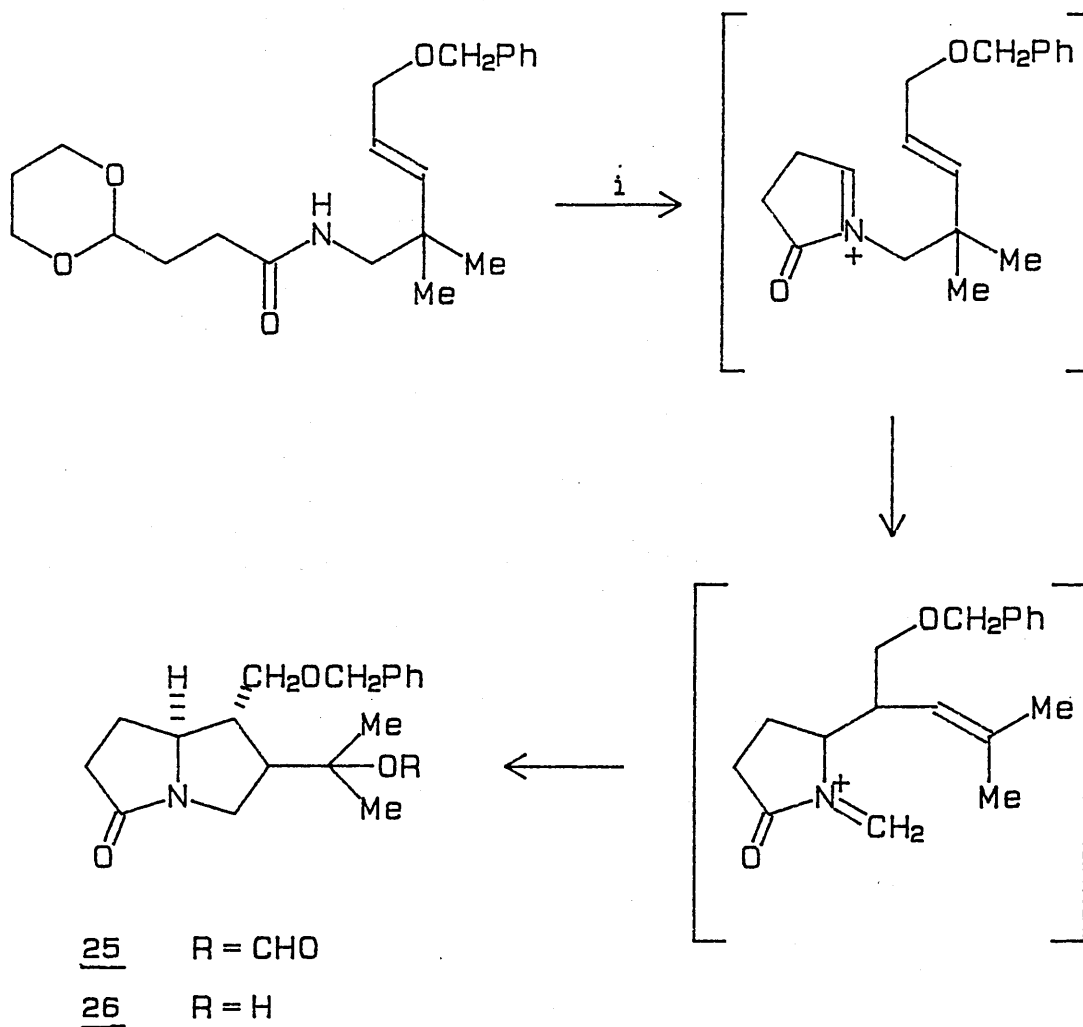
Pyrrolizidine alkaloids, like other natural products, have been a challenging goal for synthetic organic chemists. The first synthetic approaches to these compounds were made as soon as the complete structure of a number of pyrrolizidine alkaloids were established. Initially only the simplest alkylpyrrolizidines were available synthetically. However, over the past 50 years an array of synthetic methods for the construction of the pyrrolizidine ring system have been developed. Many of the earlier methods led to racemic pyrrolizidines, but, enantioselective syntheses have been developed recently.

A selection of recent publications is summarized as follows:

A. N - Acyliminium ion Cyclizations.

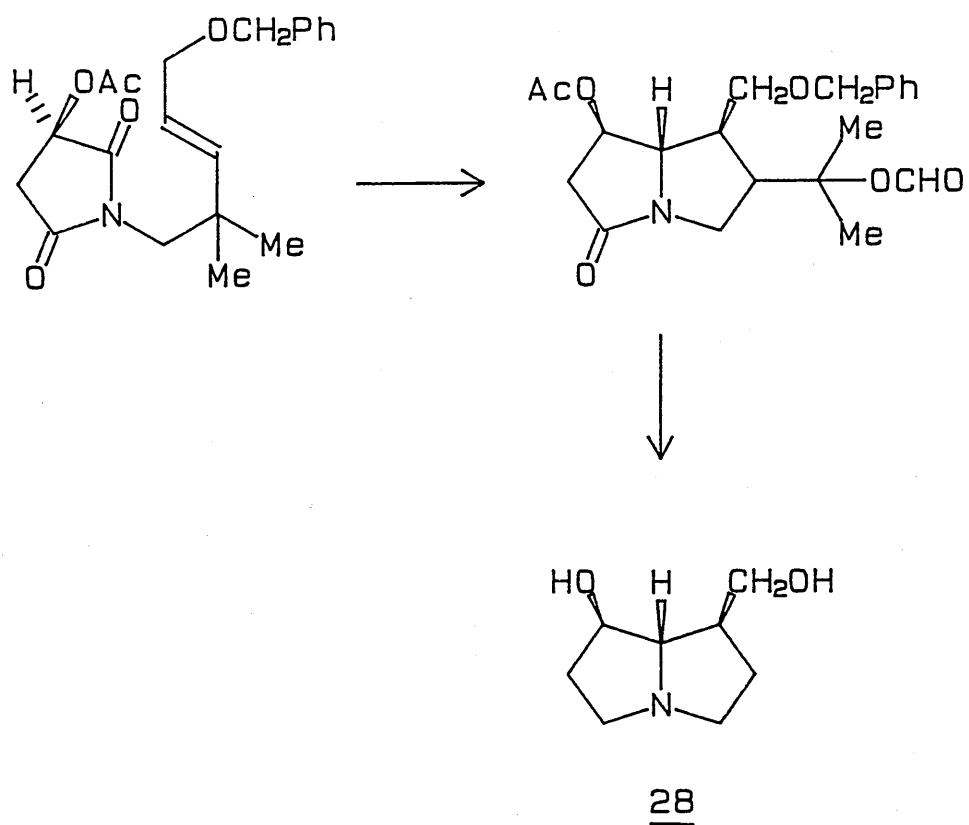
The synthesis of (\pm) - trachelanthamidine (2) and (\pm) - supinidine (11) by Hart and Yang¹³ involves an aza-Cope rearrangement of an acyliminium ion followed by cyclization to give pyrrolizidinones (25) and (26).

After completion of hydrolysis of (25) to (26), and replacement of the benzyl ether with an acetyl group, the side chain was degraded to give the iodide (27). Reduction of (27) then yielded (\pm) - trachelanthamidine (2), while dehydrohalogenation and reduction of (27) led to (\pm) - supinidine (11).

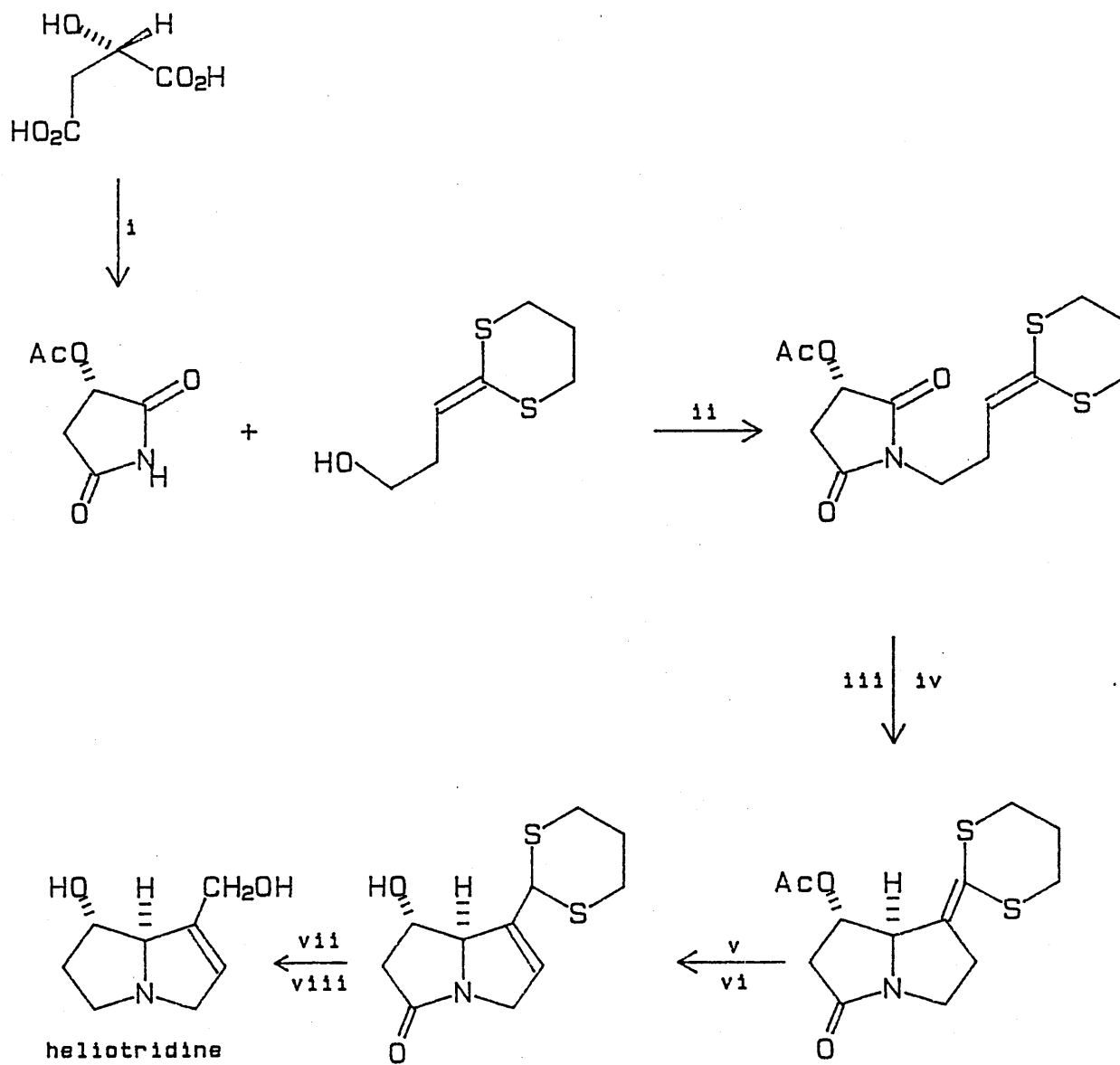


Reagents: 1, HCO₂H; 11, H₂, Pd/C, followed by Ac₂O, pyr
 111, HgO, I₂, CCl₄; iv, nBu₃SnH; v, LiAlH₄; vi, DBU.

A related strategy has been applied to the synthesis of (-) -
hastanecine¹⁴ (28).

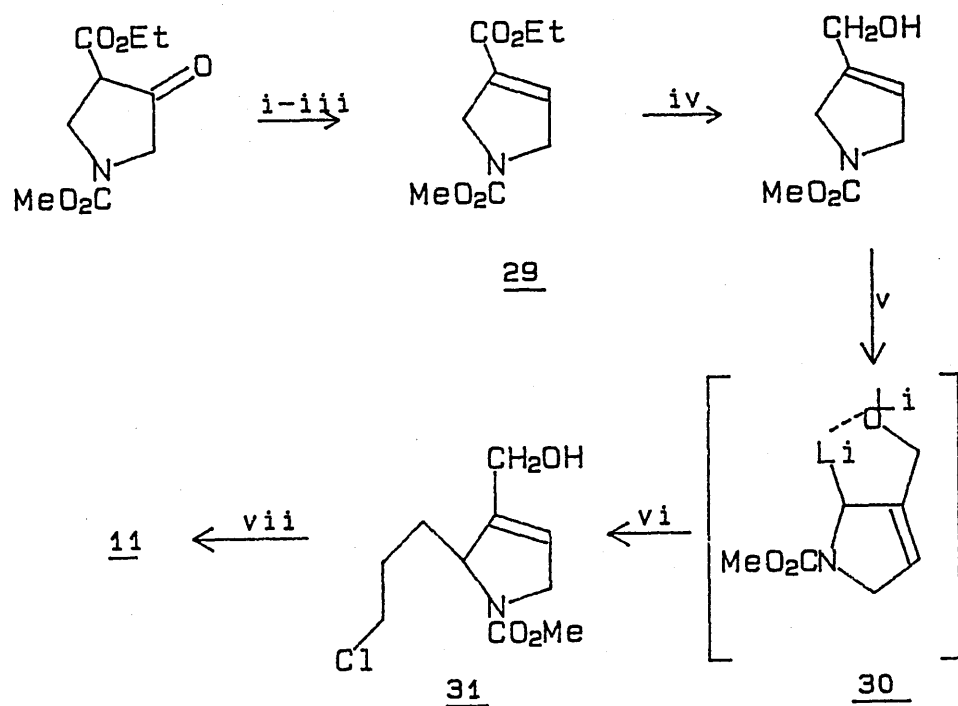


(S) - Malic acid is used in the synthesis of (+) - heliotridine by
Chamberlin and Chung.¹⁵



Reagents: 1, AcCl, then NH₃, then AcCl; 11, Ph₃P, DEAD; iii, NaBH₄;
 iv, MeSO₂Cl, Et₃N; v, K₂CO₃, MeOH; vi, LDA, HMPA, then MeOH;
 vii, HgCl₂, aq. MeCN, CaCO₃; viii, LiAlH₄

macdonald and Narayanan used Vicinal annulation of a bifunctional alkylating system, generated from the 3 - pyrroline (29), in their preparation of (\pm) - supinidine (11). The dianion (30), derived from the pyrroline and presumably stabilised by internal chelation, was regioselectively alkylated to give the chloro-compound (31). Intramolecular cyclization to (\pm) - supinidine (11) was achieved after removal of the N - protecting group in (31).



Reagents; i, NaBH₃CN; ii, PhCOCl, pyr; iii, DBU;

iv, LiAlH₄;

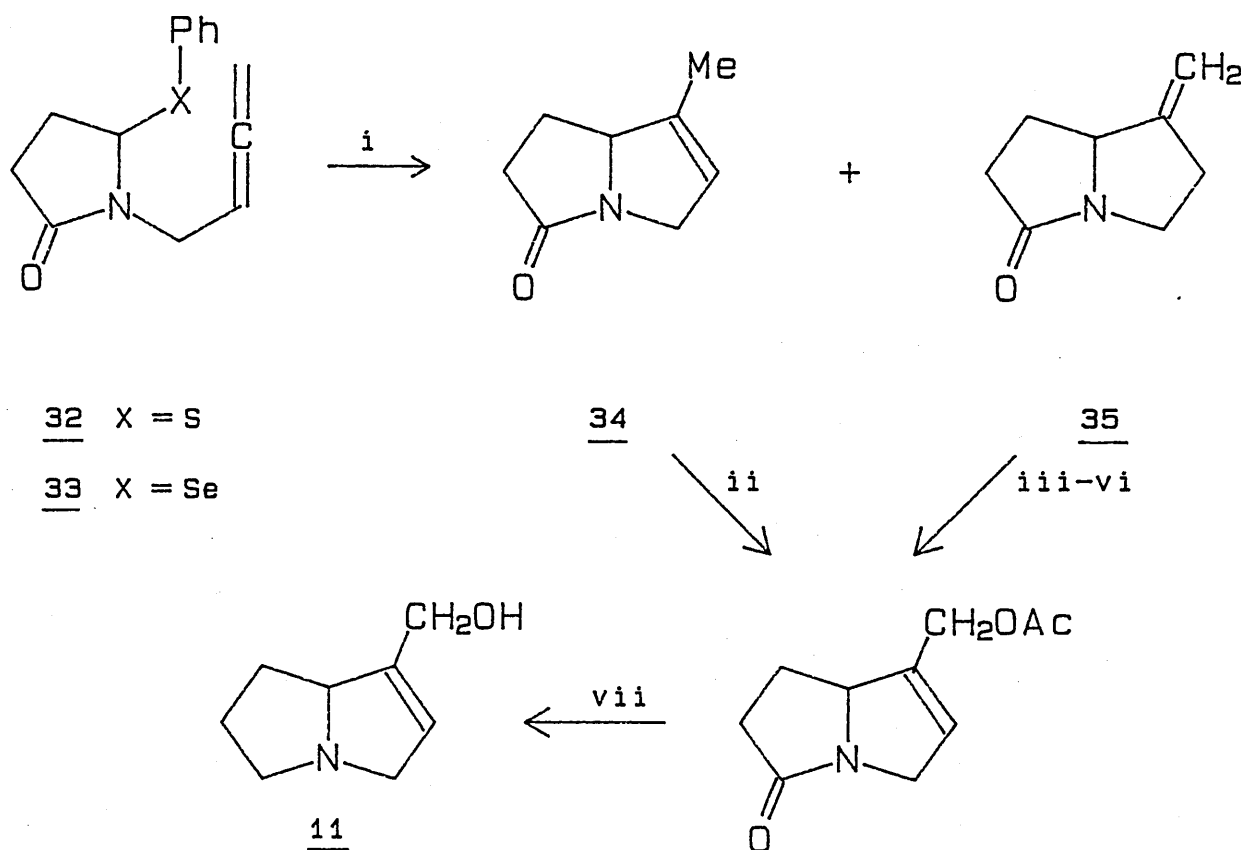
v,



vi, Br (CH₂)₃Cl;

vii, MeLi

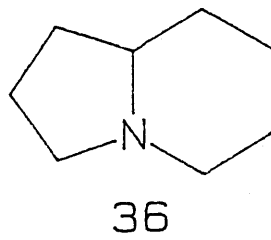
Allenes have been utilised as the unsaturated components of radical cyclization.¹⁷ The desired radicals could not be generated from the phenylthio - derivative, (32) but the phenylselenenyl - lactam (33) did act as a radical precursor, and intramolecular cyclization gave the pyrrolizidinones (34) and (35) in yields of 52% and 14% respectively. These diastereoisomers were separated (by chromatography on silica gel) and each racemate was converted into (\pm) - supinidine (11) as outlined below:



Reagents; i, $n\text{Bu}_3\text{SnH}$, AIBN; ii, SeO_2 , AcOH ; iii, PhSeOCOCF_3
 iv, NaHCO_3 ; v, H_2O_2 ; vi, Ac_2O , Et_3N , 4-DMAP vii, LiAlH_4

1.2.1. Background

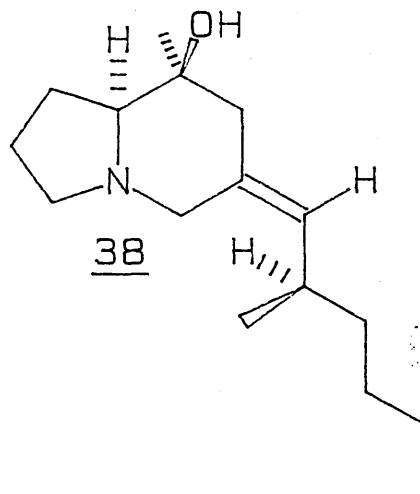
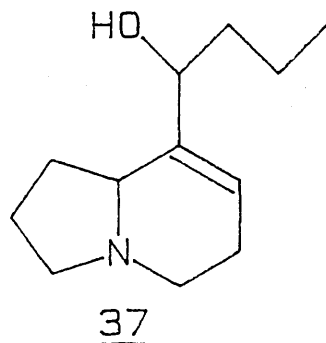
The indolizidine alkaloids, incorporating the 1-azabicyclo [4.3.0.] nonane ring system, (36) comprise a rather large group of compounds isolated from diverse natural sources, and show an interesting range of biological activity.



Some of the families containing this 5-6-fused system include:

Ipomoea alkaloids, Elaeocarpus alkaloids, Tylophora alkaloids, Slaframmine, Dendrobatid alkaloids, Prosopis alkaloids, Swainsona alkaloids, etc., etc.¹⁸

The abundance of alkaloids possessing this saturated indolizidine skeleton makes generalization difficult. We will therefore consider only two of these families: The Elaeocarpus alkaloids, represented by Elaeokanine B¹⁹ (37) and the Dendrobatid alkaloids, represented by the toxin 251 D²⁰ (38).



There are over two hundred species of the genus *Elaeocarpus* of the family *Elaeocarpaceae*. Chemical examination of these plants, which mainly occur in tropical regions, revealed a new group of indolizidine alkaloids.

The *Elaeocarpus* Alkaloids can be divided into 4 groups:

The C¹⁶ Aromatic Alkaloids

The C¹⁶ Dienone Alkaloids

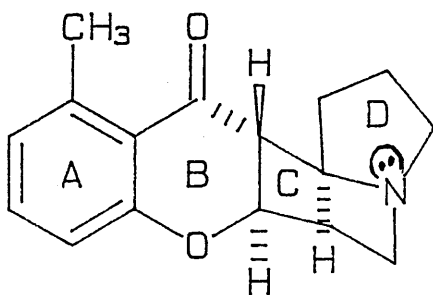
The C¹² Alkaloids of *Elaeocarpus kaniensis*

Elaeocarpidine

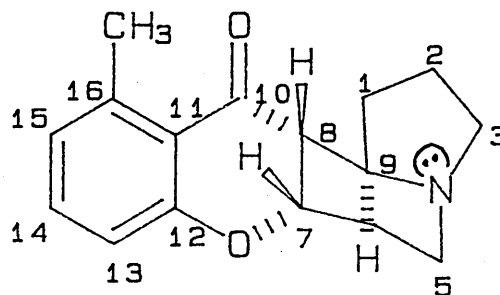
The C¹⁶ Aromatic Alkaloids

The Alkaloids (±) - *elaecarpine* (39) and (±) - *isoelaecarpine* (40) are easily interconverted isomers of molecular formula

C₁₆H₁₉NO₂.

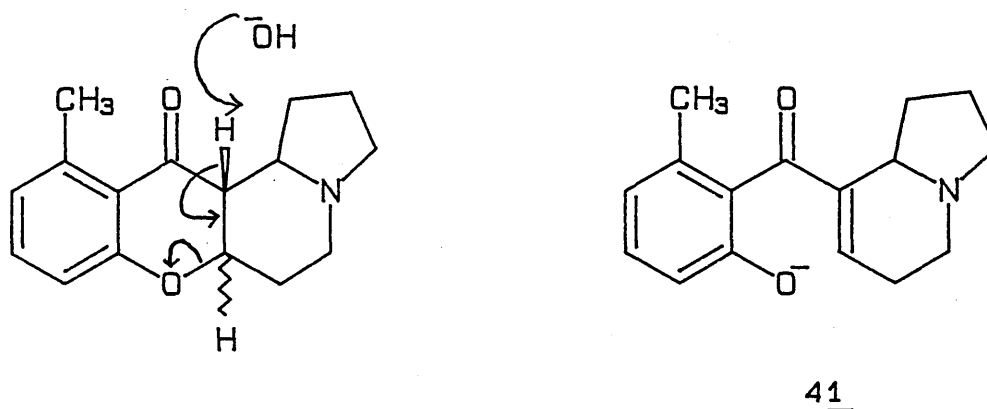


39



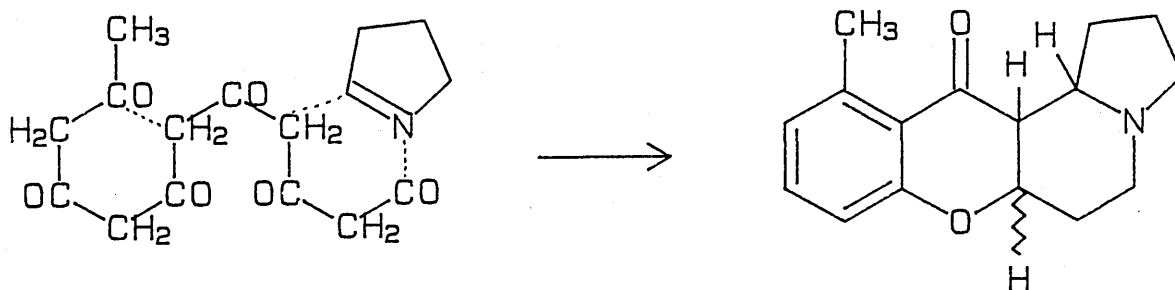
40

that of the optically pure forms, and are therefore virtually racemic. Note that structures (39) and (40) represent only one of the enantiomers of each alkaloid and therefore show relative not absolute configurations. When each alkaloid is dissolved in methanolic potassium hydroxide solution it is converted into the other alkaloid, and at equilibrium an approximately 1:1 mixture results from either base. It has been suggested that this base-catalysed epimerization proceeds by enolization at C-8 followed by breaking of the C7-O bond to give an intermediate (41) which on recyclization affords both (39) and (40).²¹



The indolizidine systems of the thermodynamically more stable isomers have a chair form for ring C with C9-H axial and trans to the lone pair orbital on the nitrogen and at each C-8 centre, C8-H is axial and the bulky system linked through the carbonyl group is equatorial.

ornithine unit and a C¹² polyketide unit (Scheme 3).

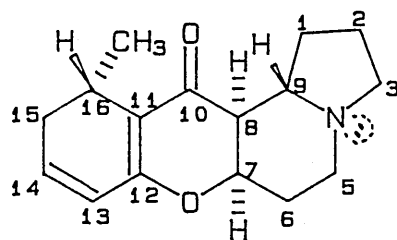


SCHEME 3

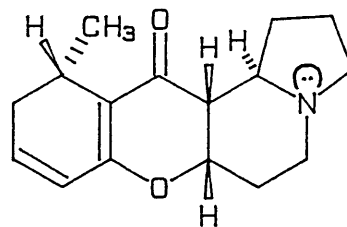
The C¹⁶ Dienone Alkaloids

There are several isomeric dienone alkaloids of molecular composition C₁₆H₂₁NO₂. (See page 26)

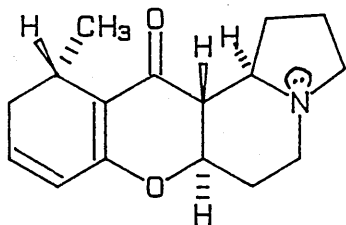
The proposed biosynthetic pathway²² again involves condensation of an ornithine unit and a C¹² polyketide unit (Scheme 3).



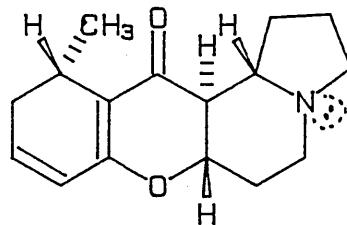
(-)-Isoelaecarpiline (42)



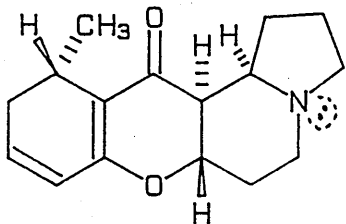
(+)-Epi-isoelaecarpiline (43)



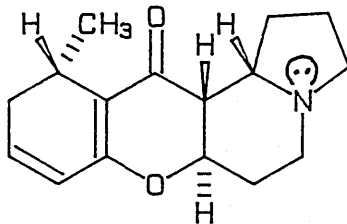
(+)-Elaecarpiline (44)



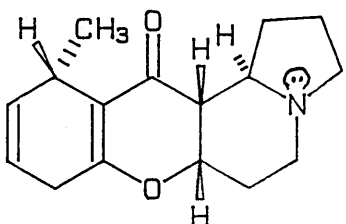
(-)-Epi-elaecarpiline (45)



(+)-Epialloelaecarpiline (46)

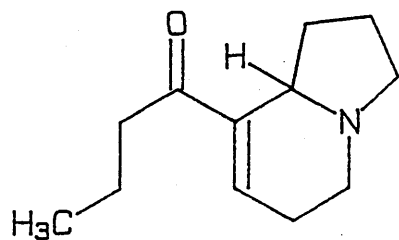


(-)-Alloelaecarpiline (47)

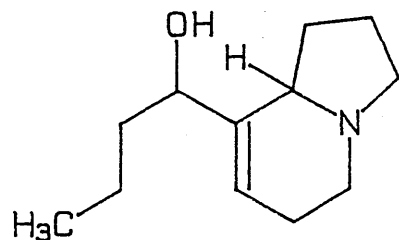


Pseudoepi-isoelaecarpiline (48)

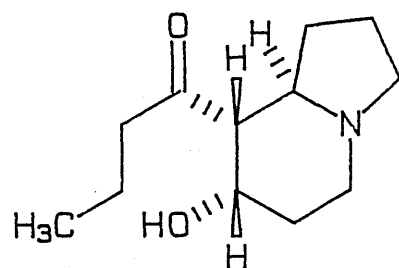
These alkaloids differ from the other known *Elaeocarpus* alkaloids in having a C¹² skeleton. There are two groups - the elaeokanines and the elaeokanidines which have, respectively, one and two nitrogen atoms.



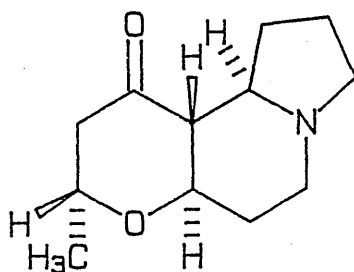
Elaeokanine A (49)



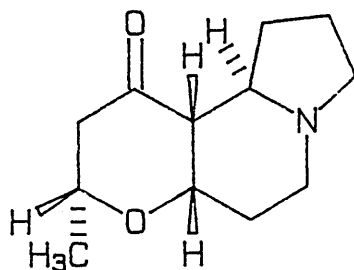
Elaeokanine B (37)



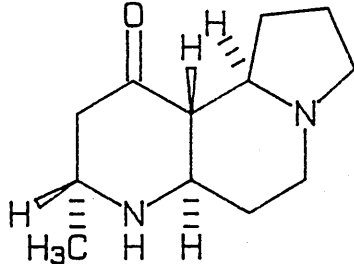
Elaeokanine C (50)



Elaeokanine D (51)

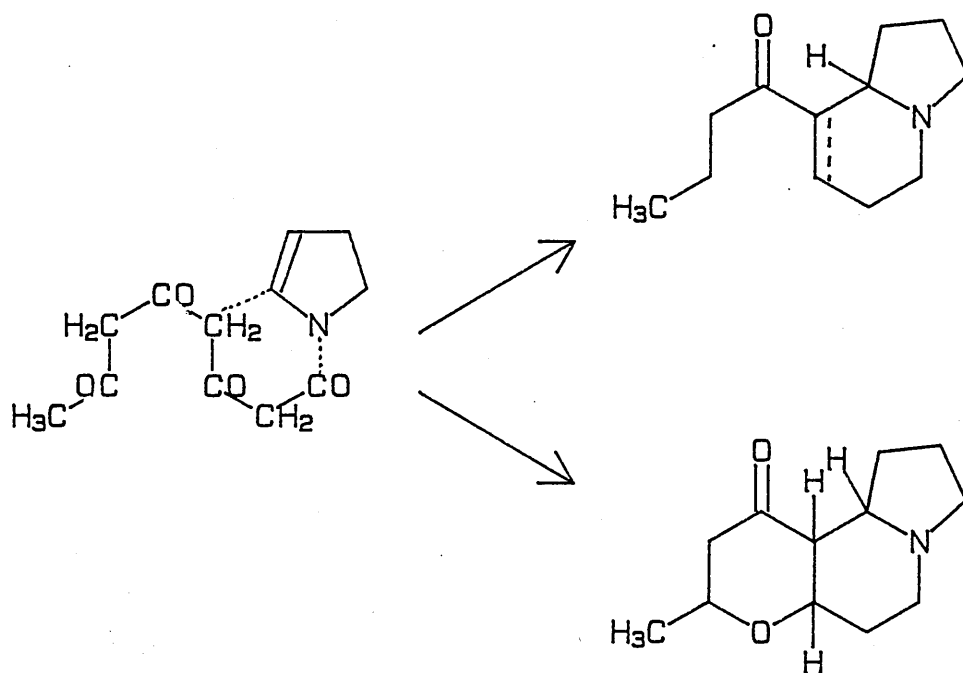


Elaeokanine E (52)

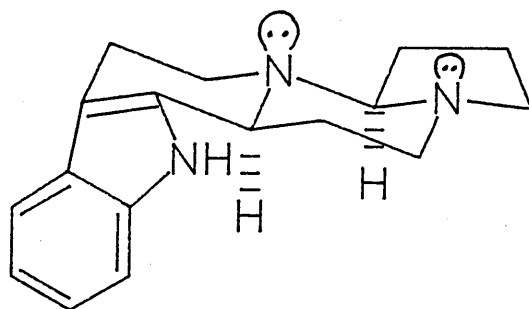


Eleaokanidine A (53)

These C¹² alkaloids are thought to be derived from ornithine and a C⁸ polyketide.



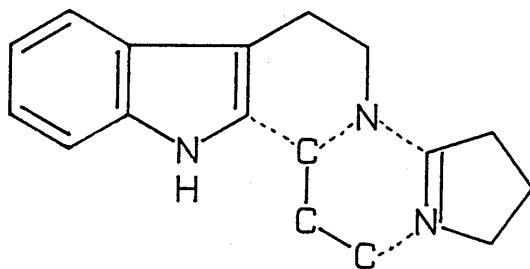
Elaeocarpidine is the only indole alkaloid isolated from *Elaeocarpus* species.



54

The structure as shown with each nitrogen lone pair trans diaxial to the hydrogen at the respective adjacent ring junction was favoured on conformational grounds²³ and has been supported by additional spectroscopic data.²⁶

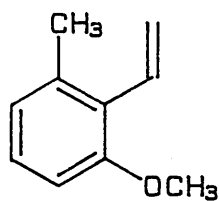
Elaeocarpidine is considered to be derived from ornithine, tryptamine and a C³ unit.²³



Although *Elaeocarpus* alkaloids are members of a relatively new major class of indolizidine alkaloids, there are many syntheses of the different members of this class, some of which are summarised below:

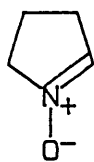
A. *Elaeocarpus* Alkaloids from Nitrones²⁷

The addition of nitrone (55) to the hindered styrene (56) affords isoxazolidine (57). Through a standard procedure of steps the amino ketone (58) is produced in good overall yield. A facile Michael reaction involving acrolein followed by a cleavage of the methyl ether with boron tribromide affords a readily separable mixture of *elaecarpine* (39) and *isoelaecarpine* (40).

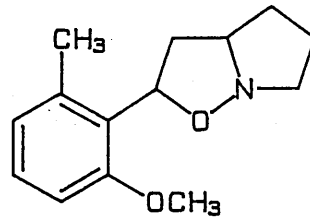
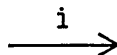


56

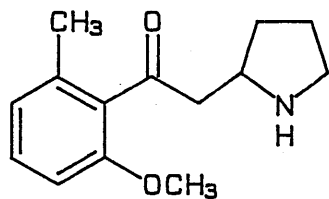
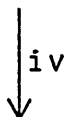
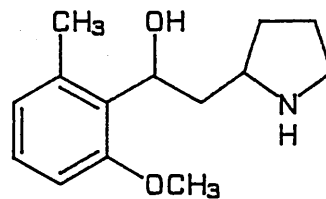
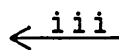
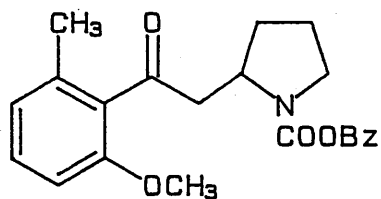
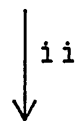
+



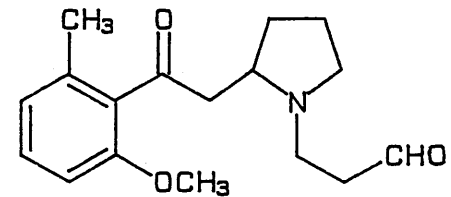
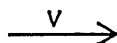
55



57



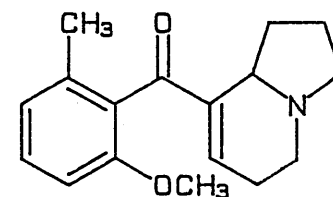
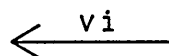
58



39

+

40



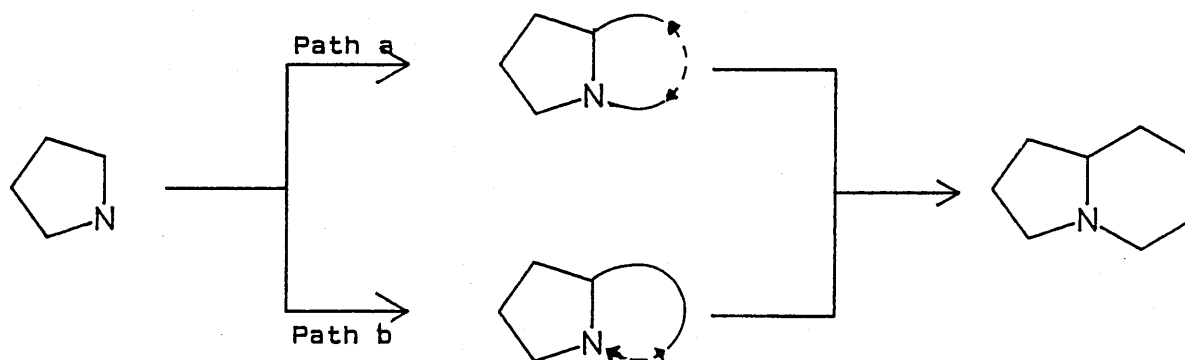
Reagents: i, Toluene, 85 C; ii, H₂/PtO₂;

iii, BzOCOC1, pyr. followed by Collins; iv, H₂/Pd-C; v, Acrolein; vi, BBr₃

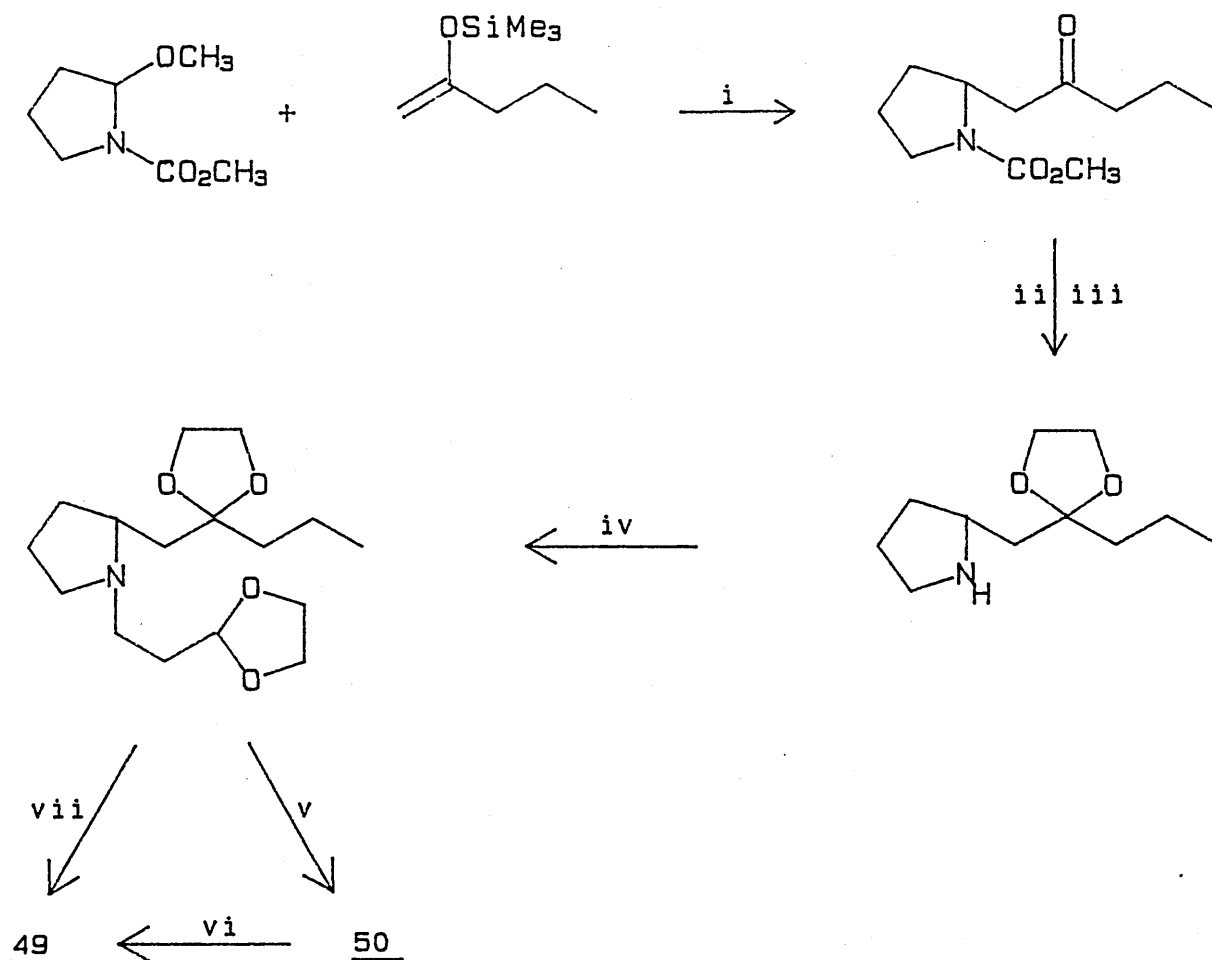
has been synthesised in a similar fashion.

B. 1,2-annulation utilising anodically prepared 1-(alkoxycarbonyl)-2-methoxypyrrolidines as key intermediates.²⁸

The construction of the indolizidine skeleton was achieved via 1,2-annulation on a pyrrolidine ring (path a or b).



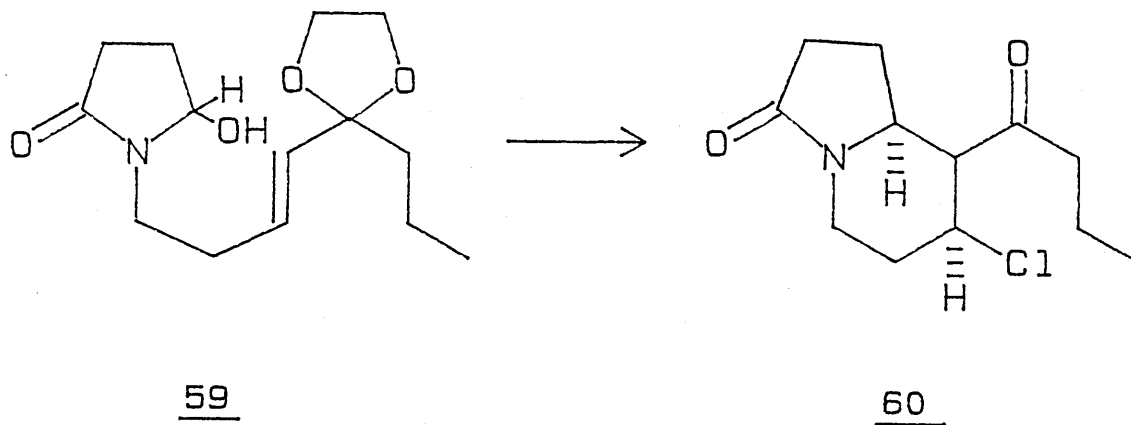
Both elaeokanine A (49) and elaeokanine C (50) were prepared in five steps from 1-(methoxycarbonyl)-2-methoxypyrrolidine.



Reagents: 1TiCl₄, CH₂Cl₂; ii, HOCH₂CH₂OH, TsOH, CH(OEt)₃, reflux;
 iii, NH₂NH₂, KOH, HOCH₂CH₂OH, reflux; iv, BrCH₂CH₂CH₂Br, NaH, DMF, 0°C;
 v, conc. HCl; vi, aq. NaOH, reflux; vii, 1M HCl, reflux, then NaOH, reflux

C. α -Acyliminium ion synthesis of Elaeokanine B.²⁹

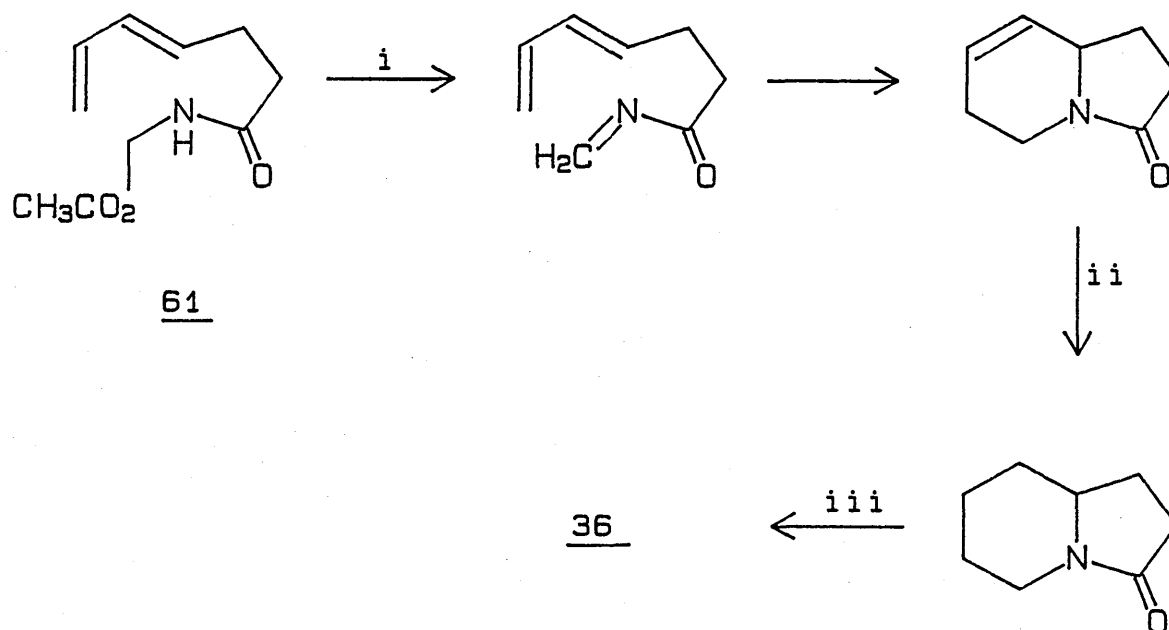
Elaeokanine B (37) has been synthesised utilising the acid-catalyzed cyclisation of hydroxylactam (59) as key step in the formation of the chloride (60).



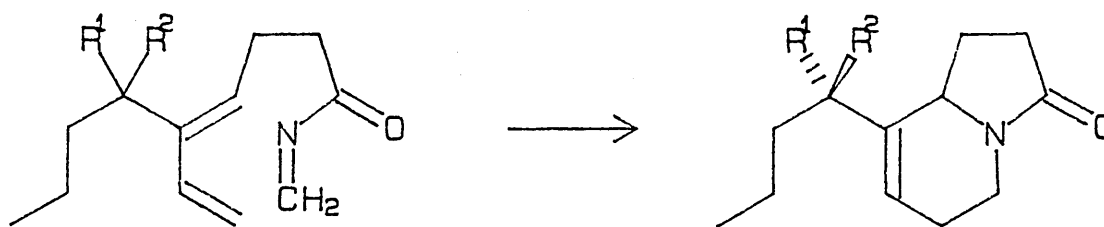
The synthesis was completed by dehydrohalogenation followed by reduction with sodium borohydride.

D. Intramolecular Imino Diels-Alder Reactions.³⁰

δ -Coniceine (36) was prepared from Diene-methylol acetate (61).



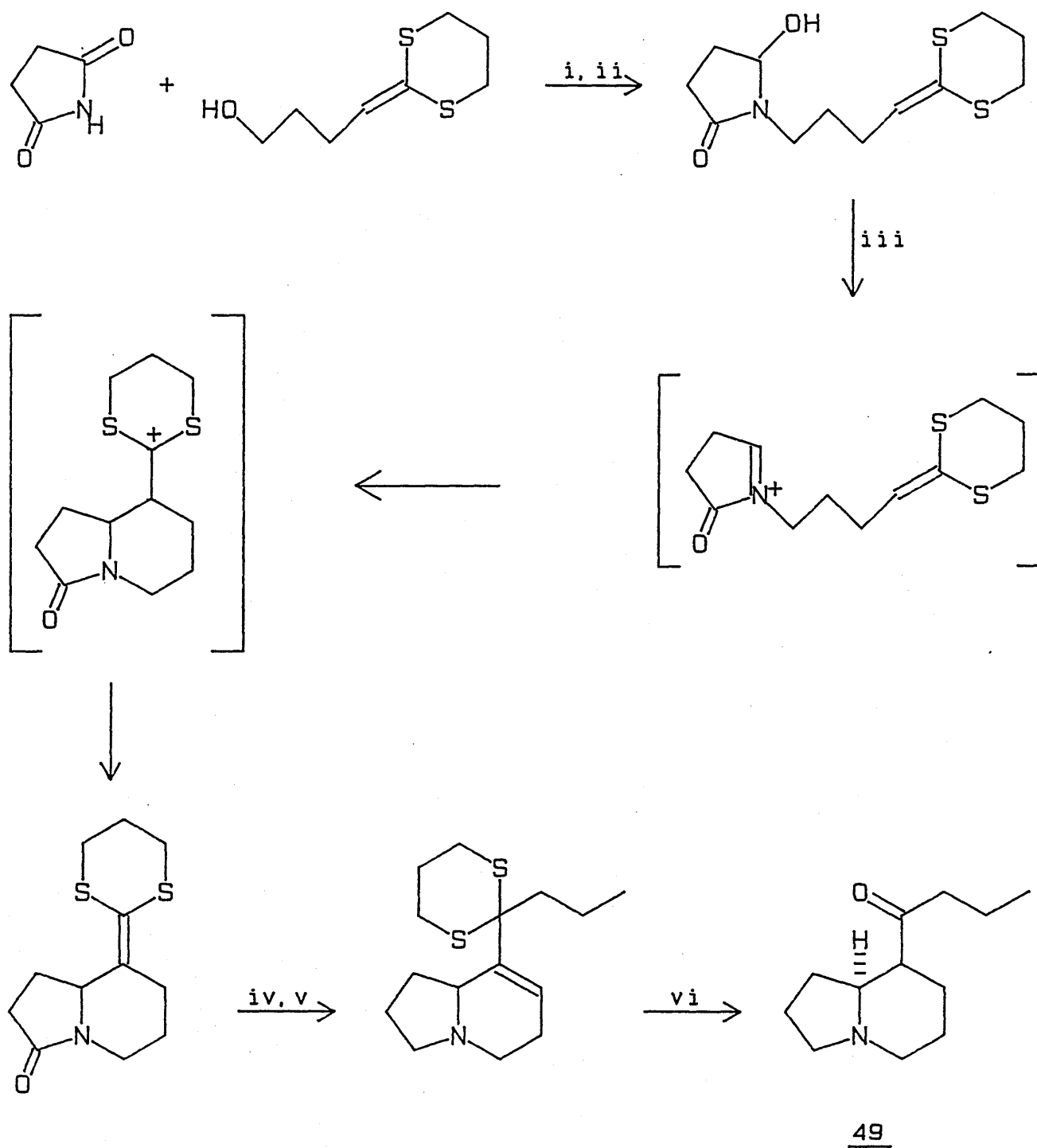
Reagents: i, heat, (-HOAc); ii, H₂/Pd-C; iii, Borane/THF



These bicyclic lactams can then be readily converted into (49) and (37).

E. Acyliminium ion cyclization.³¹

Elaeokanine A (49) has been synthesised utilising an acetoxy - directed acyliminium ion-ketene dithioacetal cationic cyclisation.

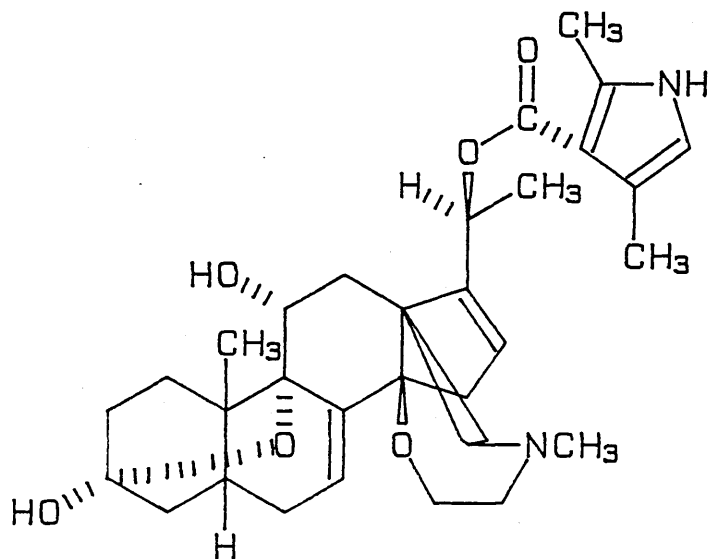


Reagents: i, Ph_3P , THF, then DEAD; ii, NaBH_4 , MeOH at -40°C then aq. NaHCO_3 , CH_2Cl_2 ;
 iii, MsCl , Et_3N ; iv, LiAlH_4 ; v, LDA, PrI; vi, HgCl_2 , CaCO_3 , aq. MeCN, at -50°C

Poisons for arrows and blow darts have been derived from a wide variety of sources in both the plant and animal kingdoms. One unique source of such poisons is the skin secretion of certain brightly coloured frogs (Dendrobatidae) native to the rain forests of Western Columbia. It is not surprising that the nature and action of the poison from these frogs has attracted the attention of toxicologists, pharmacologists and chemists. Some twenty years of research has led to the conclusion that the active principles of the poison-dart frogs are extremely toxic alkaloids. Virtually all these alkaloids possess high pharmacological activity on nerve and muscle. Structures for five classes of dendrobatid alkaloids have been elucidated:

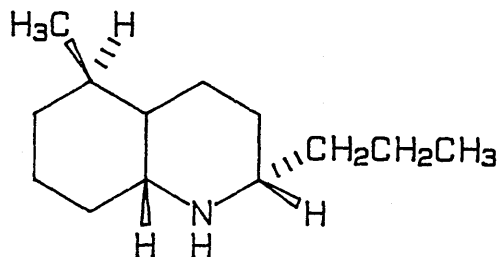
The Batrachotoxins

After five years of research, the structures of the first class of dendrobatid alkaloids were reported in 1968-69. They were all closely related complex steroidal alkaloids (see 62), whose presence in nature still remains unique to the Columbian poison-dart frog, *Phyllobates aurotaenia*.



Pumiliotoxin-C

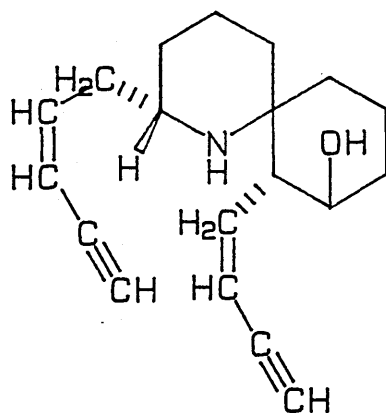
Extension of these investigations to other poison frogs of the Dendrobatidae family led to the isolation of simpler alkaloids. The structure of the first of the simpler alkaloids was reported in 1969. The compound was proved to be a cis-decahydroquinoline and was named pumiliotoxin-C (63). Although termed a toxin, the compound has relatively low toxicity.



63

Histrionicotoxins

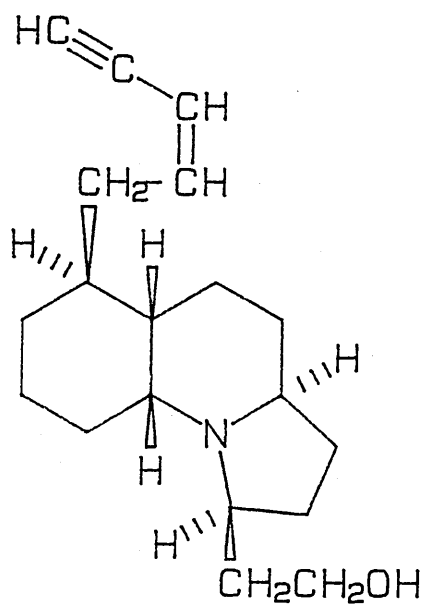
Preliminary studies of another poison frog, *Dendrobates histrionicus*, indicated the presence of another class of relatively simple alkaloids. The structures of these were reported in 1971 and were proved to be unique spiropiperidine alkaloids with remarkable acetylenic and allenic centres of unsaturation in the side chain substituents. The parent compound was named histrionicotoxin (64) after the specific name of the frog from which it was first isolated. A number of histrionicotoxins were subsequently isolated and structurally defined. Like pumiliotoxin-C, the histrionicotoxins exhibit relatively low toxicity to mammals.



64

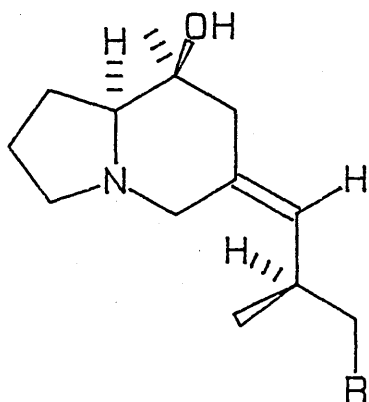
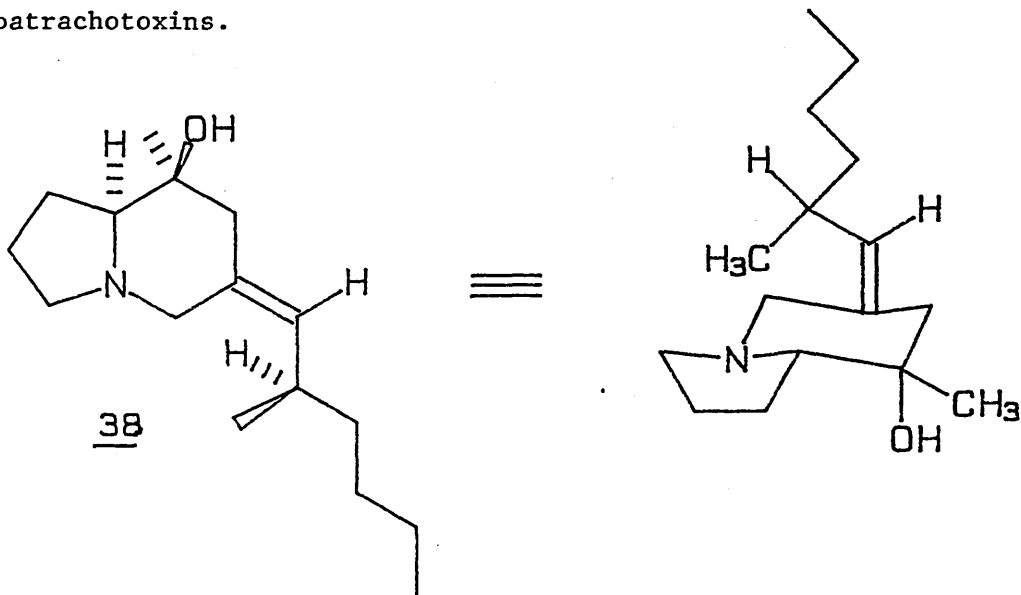
Gephyrotoxins

One of the major alkaloids from *Dendrobates histrionicus* proved to be a tricyclic alkaloid which after elucidation of its structure was named gephyrotoxin (65). Again gephyrotoxin exhibits relatively low toxicity to mammals.



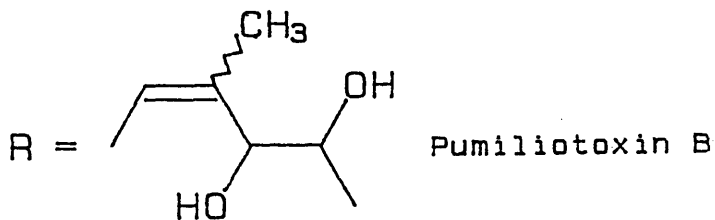
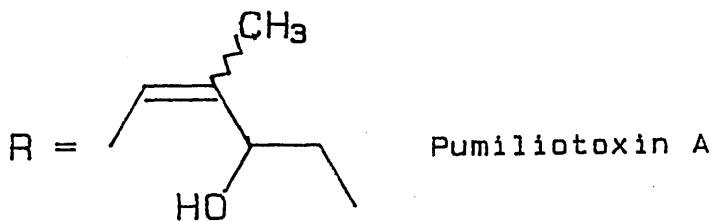
65

The structural nature of alkaloids of the pumiliotoxin-A class remained an elusive challenge for many years. The structure of a relatively simple member of the class, designated 251D (38) was finally elucidated in 1980.³³ The compound proved to be an indolizidine and its structure provided the key to the structures of pumiliotoxin-A, pumiliotoxin-B, and a few further alkaloids of the pumiliotoxin-A class. They are relatively toxic compounds, although at least two orders of magnitude less toxic than the batrachotoxins.



R = CH₂CH₂CH₃ 251D

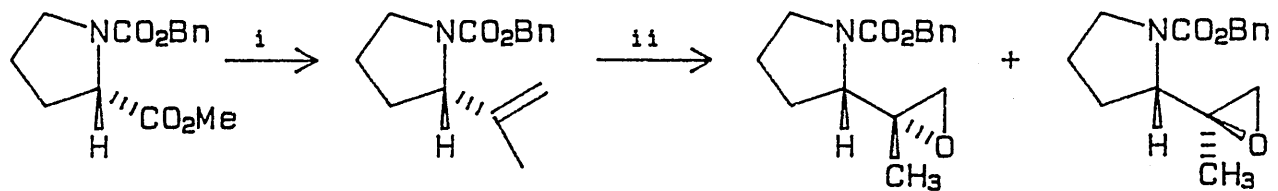
R = CH₂CH₃ 237A



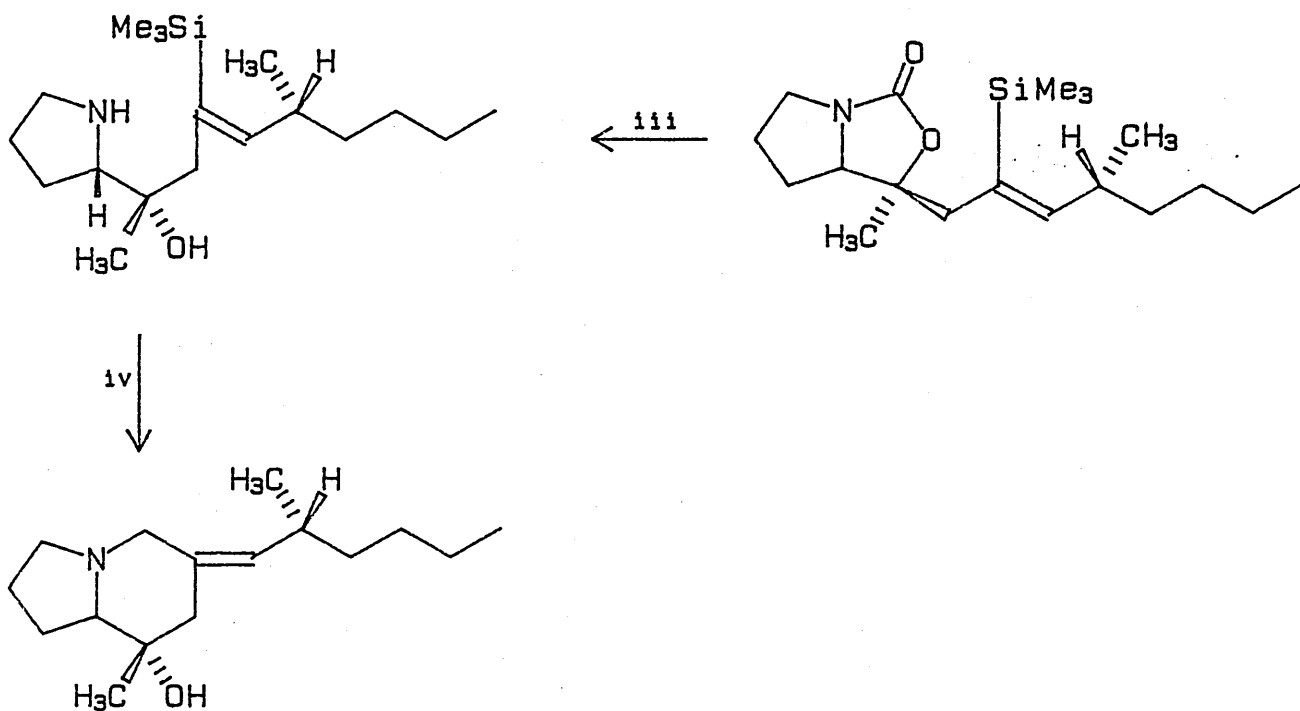
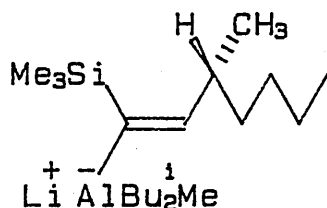
indolizidine (1-azabicyclo [4.3.0.] nonane) ring system and differ only in the side chain. This class of Dendrobatid Alkaloids is of more interest to us since we are concerned with indolizidine synthesis.

Dendrobatid Alkaloid Synthesis (Pumiliotoxin-A class)

The first enantiospecific total synthesis of 251D (38) was achieved in 10 total steps from 1-heptyn-3-one and N-carbobenzyloxy-L-proline methyl ester (66) with an overall yield of 6%.²⁰ The synthesis defines a concise and enantiospecific procedure for preparing the pumiliotoxin - A alkaloids from L - proline and also introduces a new, and potentially general, method for forming unsaturated azacyclic rings.



66



Reagents: i, MeMgI followed by SOCl_2 , pyr., THF at -45°C ;

ii, mcpba, CH_2Cl_2 , 25°C ; iii, 20% KOH, MeOH- H_2O , reflux;

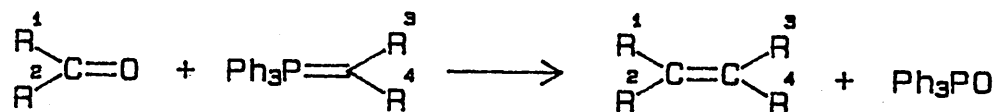
iv, paraformaldehyde, EtOH, d-10-camphorsulphonic acid

CHAPTER 2

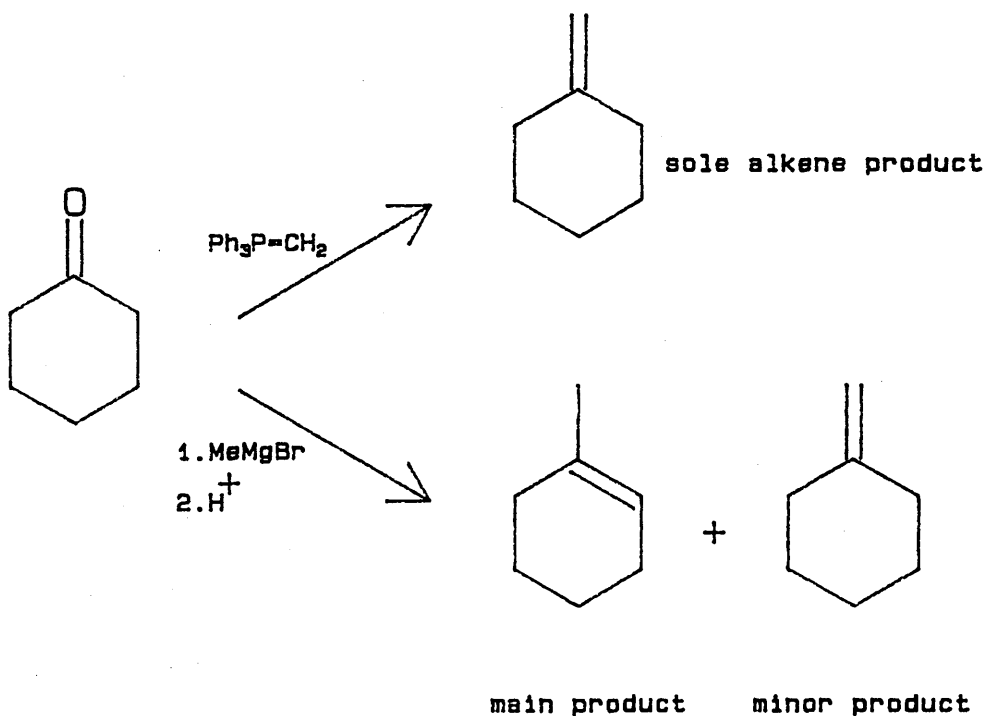
Cycloalkene Synthesis by Intramolecular Wittig Reaction

- 2.1. Introduction
- 2.2 Wittig reactions utilising vinylphosphonium salts,
vinylphosphonates and vinylphosphine oxides
- 2.3 Wittig reactions utilising cyclopropylphosphonium salts
- 2.4 Wittig reactions utilising butadienylphosphonium salts
- 2.5 Approaches to the synthesis of pyrrolizidines and
indolizidines via intramolecular Wittig reactions

The Wittig reaction (the condensation of a carbonyl compound with an alkylidenetriphenylphosphorane to give an olefin and triphenylphosphine oxide), has become one of the favourites among the numerous methods of olefin synthesis:³⁴

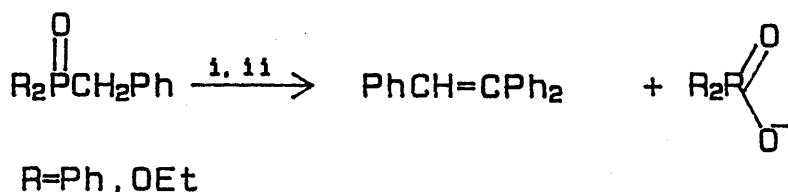


One of the main virtues, in marked contrast with other alkene syntheses is the fact that no ambiguity exists concerning the position of the newly formed carbon-carbon double bond. Even when it occupies an energetically unfavourable position, the double bond always appears at the site of the former carbonyl group. An example of this regioselectivity is the preparation of methylene-cyclohexane:³⁵



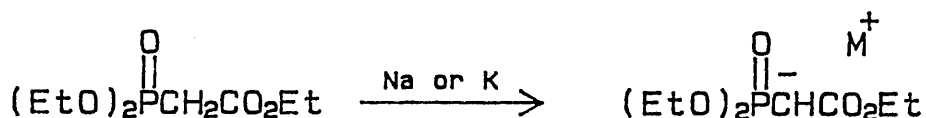
predictable, and mixtures of (E) - and (Z) - alkenes are often produced if the ylide and carbonyl compound are both unsymmetrically substituted. This, however, may be influenced to a considerable extent by choice of reaction conditions.³⁶

A useful supplement to the Wittig reaction is PO - activated olefin synthesis. In the 30 years since the original report by Horner and Wippel³⁷ of the use of PO - stabilised carbanions in olefin synthesis the reaction has come to challenge the Wittig reaction as the synthetic method of choice when a specific alkene is required:

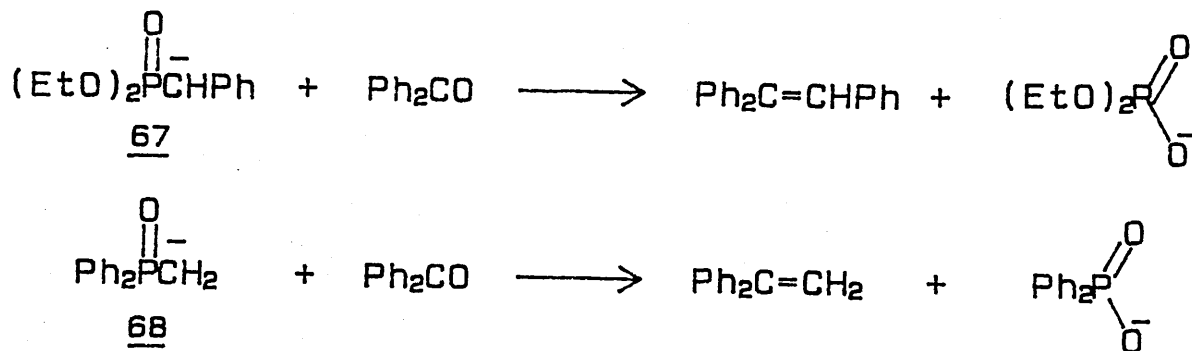


Reagents: 1, NaNH_2 , benzene; 11, Ph_2CO

The popularity of PO - activated olefin synthesis is shown by the profusion of publications which can be traced back to 1927 when Arbusov³⁸ showed that the phosphonate group would stabilise an adjacent carbanion which in turn could be alkylated by a variety of reagents:



olefination reaction involved the reaction of phosphonate - (67) or phosphonyl - (68) stabilised carbanions with benzophenone to give the corresponding olefin by elimination of dialkyl phosphate or diarylphosphinate, respectively:



Compared to the Wittig reaction the PO - activated reaction has a number of advantages:⁴⁰

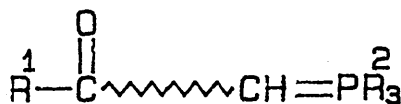
(a) PO - stabilised carbanions are much more nucleophilic than the corresponding phosphonium ylides, so they react with a wider range of carbonyl compounds under milder conditions. The ease of alkylation and acylation of PO - stabilised carbanions offers a convenient route to α - substituted reagents. However, the phosphoryl and phosphonyl group has a less stabilising effect and so electron-withdrawing α - substituents are generally required at the carbanion centre before preparative yields of olefin can be obtained.

(b) A major problem in the Wittig reaction is separation of the alkene and phosphine oxide products. The phosphinic, phosphonic, and phosphoric acid derivatives obtained from PO - activated synthesis are all soluble in water, so separation from the olefin is easily achieved.

trans-stereochemistry but recent developments suggest that considerable control of stereochemistry is possible.

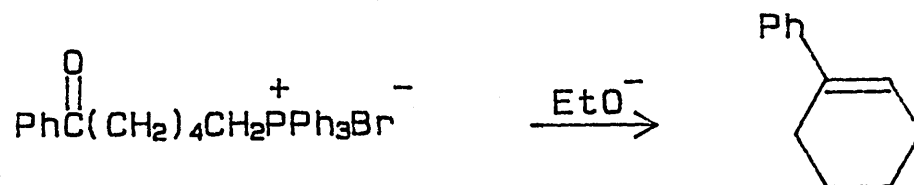
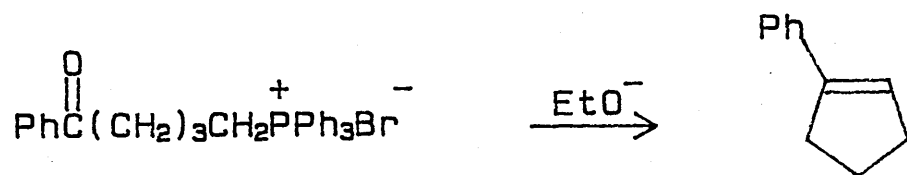
Surprisingly, no name or combination of names has become generally accepted to describe PO activated olefin synthesis, and Horner-Wittig, Horner, Emmons, Wadsworth-Emmons etc. are all frequently used in the literature. A choice of these is not easy; while Horner³⁷ clearly published the first example of the reaction, mechanistically it is closely related to the Wittig reaction,³⁵ and Wadsworth and Emmons⁴¹ soon published an excellent paper which indicates almost every future application of the reaction. However, Wittig has given his name to the original olefin synthesis involving phosphorus so some combination of these names seems appropriate.

This chapter is a review of intramolecular Wittig reactions,³⁴ in which a carbon-carbon double bond is formed by condensation of a carbonyl function with an alkylidenephosphorane group incorporated in the same molecule (69).

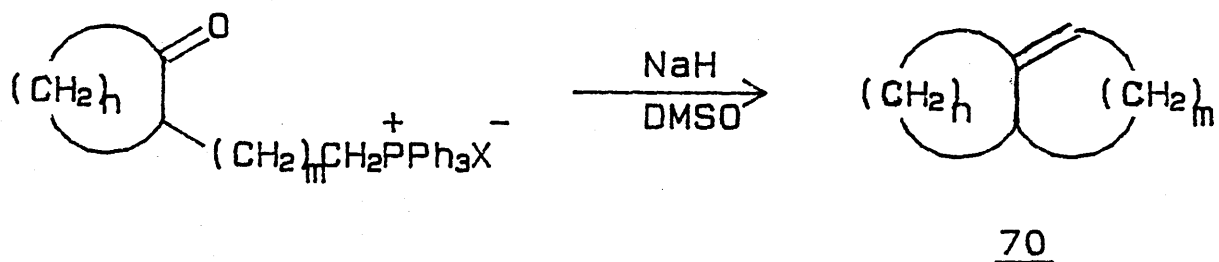


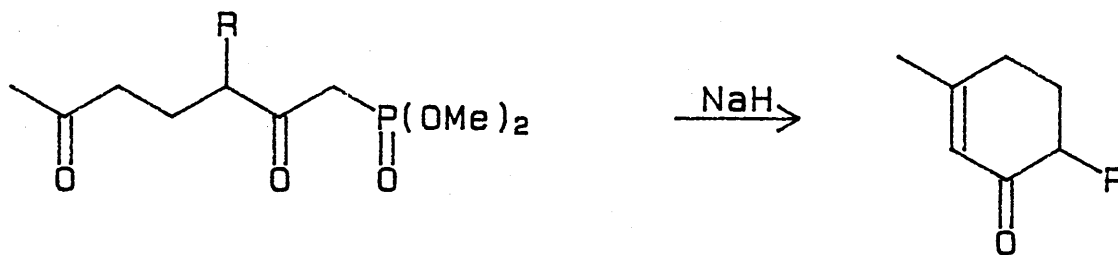
69

two independent groups:



For the synthesis of annulated bridgehead olefins (70) free of double bond isomers, the intramolecular Wittig reaction is the method of choice:





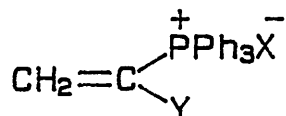
Heterocyclic alkenes can be formed by the Wittig reaction, for example:



N- and S-heterocycles can be synthesised in the same way.

In all the above reactions the ylide or phosphorus carbanion is formed by removal of the acidic α -hydrogen from a phosphorus compound. It is, however, possible to form the ylide or phosphorus carbanion in situ. This can be achieved by addition of nucleophiles to various phosphorus compounds such as vinylphosphonium salts, vinylphosphonates, vinylphosphine oxides, cyclopropylphosphonium salts and butadienylphosphonium salts.

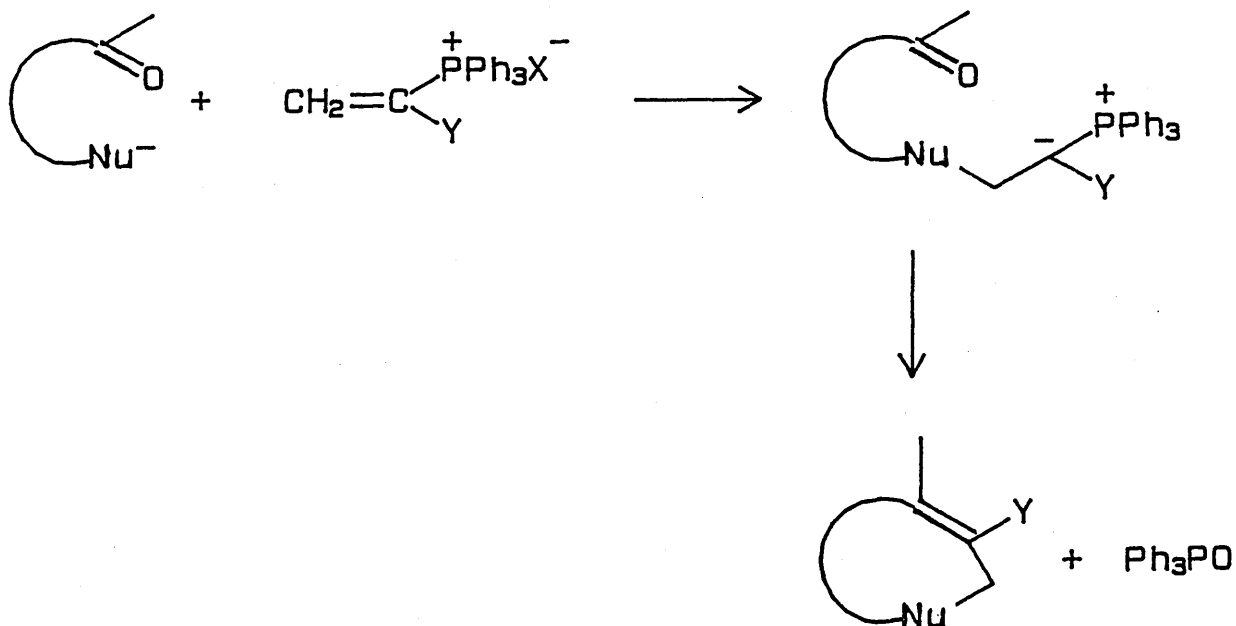
The use of vinylphosphonium salts (71) in the formation of heterocyclic, carbocyclic and chain extended systems has been of significant interest over the past 20 years.³⁴ The main reason for this has been their dual role as Michael acceptors and/or Wittig reagents for both intermolecular and intramolecular processes.



71

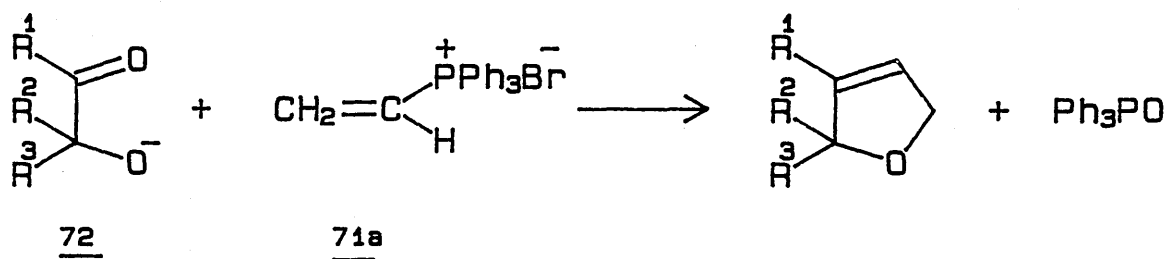
- | | | |
|---|---------|--------|
| a | Y = H | X = Br |
| b | Y = OEt | X = Br |
| c | Y = SMe | X = Cl |
| d | Y = SPh | X = I |

The vast majority of work in this area has involved the construction of cyclic systems. Their use in ring formation involves attack by a nucleophile on the vinylphosphonium salt to form an ylide which then undergoes an intramolecular Wittig reaction with a carbonyl group incorporated in the same molecule to give an olefin and triphenylphosphine oxide (Scheme 4).

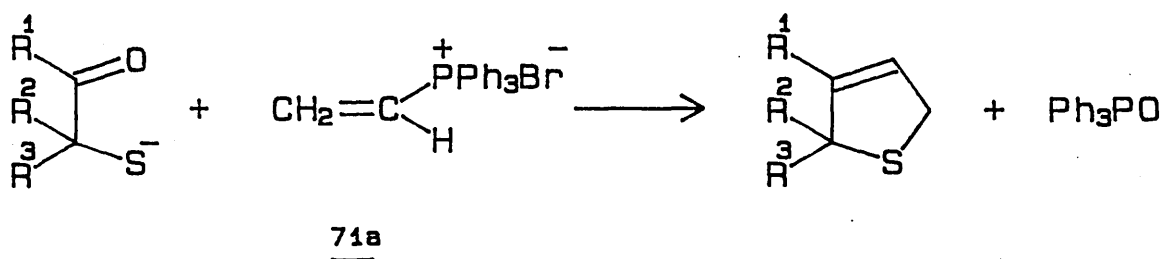


SCHEME 4

A large number of carbocyclic and heterocyclic compounds have been synthesised according to the above Scheme. For instance, the addition of the anion of an α -hydroxyketone (72) to vinyltriphenylphosphonium bromide (71a, Y=H, X=Br) eventually leads to a 2,5-dihydrofuran:

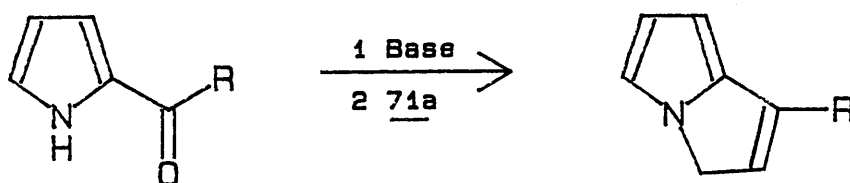
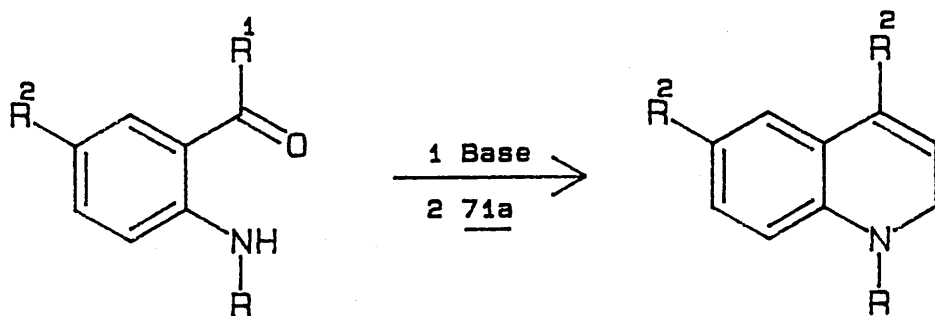


In the same way 2,5-dihydrothiophenes can also be formed:

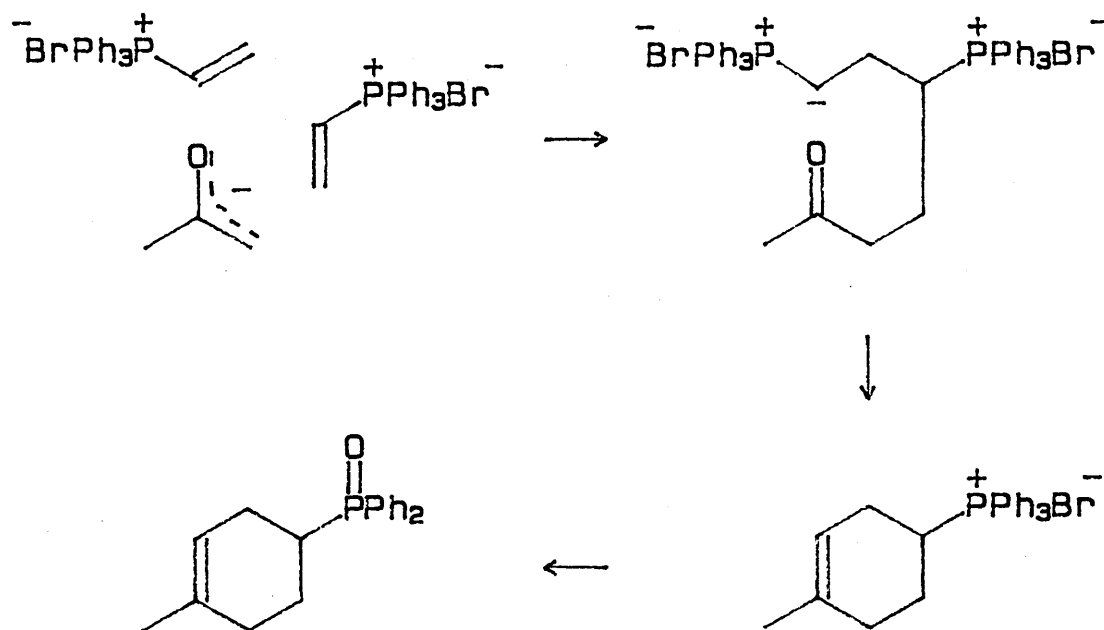


by addition reactions of nucleophiles to vinyltriphenylphosphonium

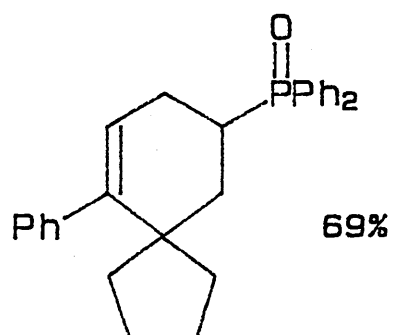
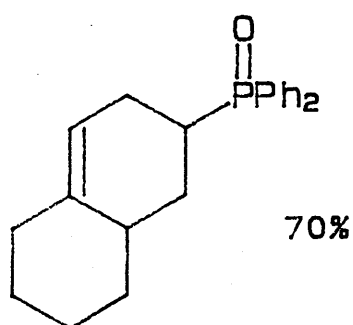
bromide (71a, Y=H, X=Br):



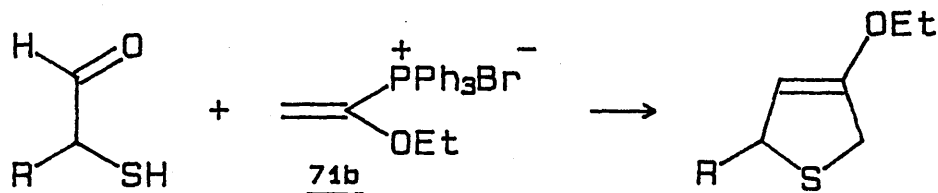
Posner⁴² has demonstrated a method for connecting three separate two-carbon units in an efficient 2+2+2 construction of some phosphorus substituted cyclohexenes. The method involves a sequential Michael-Michael-ring closure reaction effected by addition of 2 equivalents of vinyltriphenylphosphonium bromide (71a) to an enolate intermediate. The triphenylphosphonium salt formed by this reaction was then hydrolysed to the more easily handled phosphine oxide:



A variety of enolate intermediates were used to illustrate the scope of this type of reaction and all gave good yields of the phosphine oxide product. For instance:



versatile reagent and it is perhaps surprising that more use has not been made of it in natural product synthesis. This points to the fact that the major obstacle to its widespread use is that the product derived from it is an alkene which limits its use in the synthesis of complex organic molecules. It was therefore necessary to develop a more flexible reagent which would allow greater control over the introduction of functionality. Thus a substituted alkene (or vinyl derivative) was required which could be converted under mild conditions to a more useful functional group. It was thought that vinylphosphonium salts in which the α -carbon is joined to a heteroatom might be especially useful since the product of a Wittig reaction would be an enol derivative, which is easily converted into a ketone. Because of the importance of the carbonyl group in general organic chemistry, any method for the introduction of this functionality is extremely useful. A number of groups concerned themselves with this problem. McIntosh⁴³ reported the synthesis of 1-ethoxyvinyltriphenylphosphonium bromide (71b, Y=OEt, X=Br) and studied its use in the synthesis of 2,5-dihydrothiophenes.⁴⁴



Unfortunately only a low yield of the desired product was formed.

alkylthio- or arylthio-substituted vinylphosphonium salts (71c) and (71d) should give ylides of enhanced stability over the ylide derived from (71b). It has since been shown that the most useful of all vinylphosphonium salts are 1-methylthiovinyltriphenylphosphonium chloride (71c R=SMe, X=Cl) and its 1-phenylthio analogue (71d R=SPh, X=I) which were first developed in our laboratories in 1978.⁴⁵ Both (71c) and (71d) are prepared using the same procedure.⁴⁶ (Scheme 5)



When R = Me , X = Cl

R = Ph , X = I

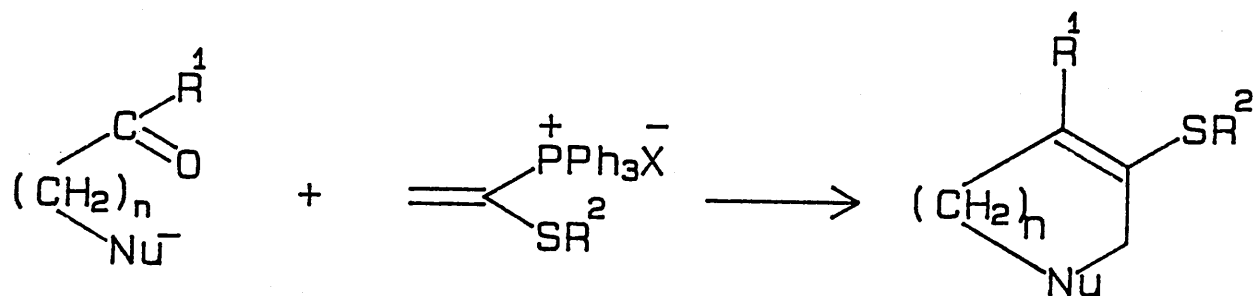
Reagents: 1, CH₃CN, reflux; 11, CH₂=N⁺(CH₃)₂Cl⁻, CH₃CN, reflux;

SCHEME 5

A slight modification of this reaction for a related salt has also recently been reported.⁴⁷

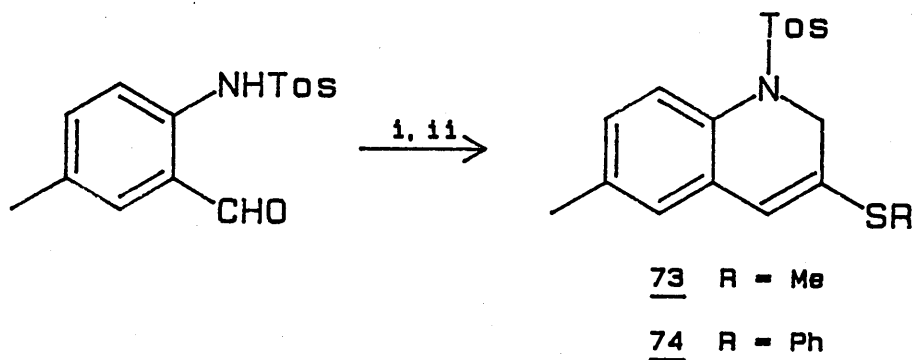
(71c) and (71d) have been shown to be useful for the formation of highly functionalised cyclopentanes^{46,48} and have been used in a number of partial and total natural product syntheses, for example prostaglandins,⁴⁹ jasmones and methylenomycins⁴⁸ chrysomelidial,^{50,51} loganin,^{50,51} hirsutene,⁵¹ and sarkomycin.^{51,52} These syntheses have been discussed in detail in the relevant references, but in each case the key point is the useful transformations that can be effected using vinylsulphides as intermediates.

(71c) and (71d) have been concerned primarily with 5-membered carbocyclic compounds (Scheme 6 Nu=C⁻, n=1).



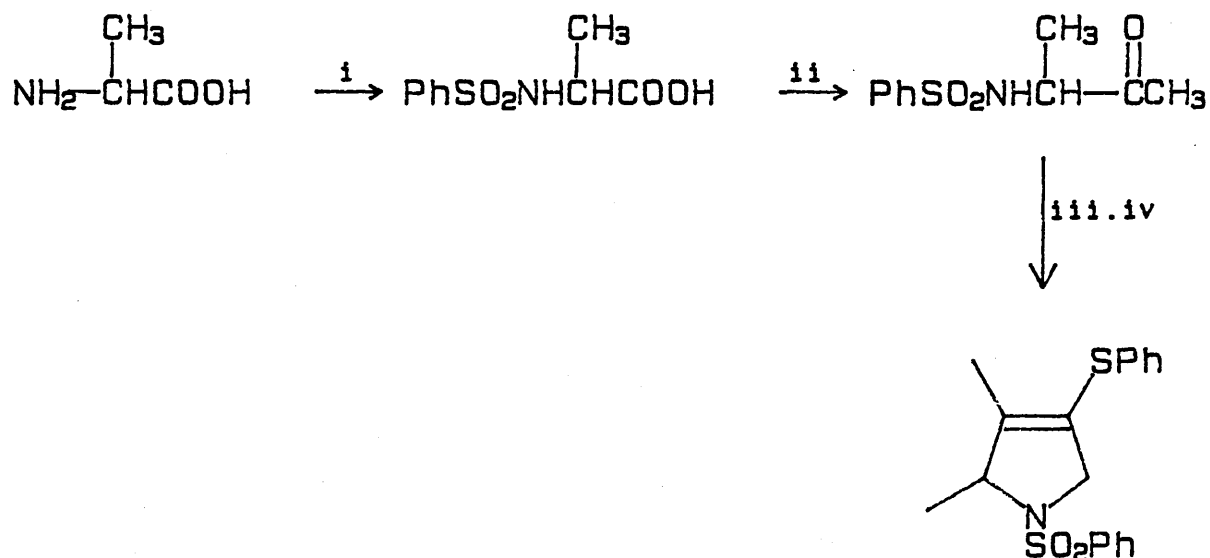
SCHEME 6

It was therefore obvious to see whether this approach could be extended to the synthesis of various heterocyclic rings (Scheme 6, Nu = N⁻, O⁻, S⁻, n 1). Investigations in this area were successful and dihydroquinolines (73) and (74) were formed in good yields.⁵³



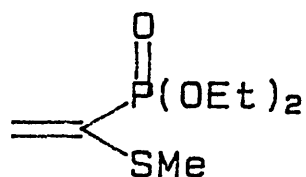
Reagents: 1, NaH, THF; 11, 71c or 71d, reflux

salts (71c) and (71d) involves the preparation of unsaturated heterocyclic compounds from α -amido (aldehydes and) ketones. At the present time this work is in its preliminary stages but the following reaction sequence has been effected.

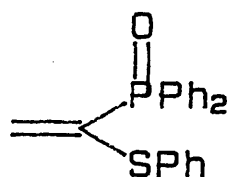


Reagents: i, NaOH, PhSO₂Cl; ii, BuLi, MeMgBr; iii, base; iv, 71d

Since the preparation of (71c) and (71d) and the demonstration of their use in the formation of highly functionalised compounds, the corresponding phosphonate⁵⁴ (75) and phosphine oxide⁵⁵ (76) have subsequently been prepared in other laboratories.

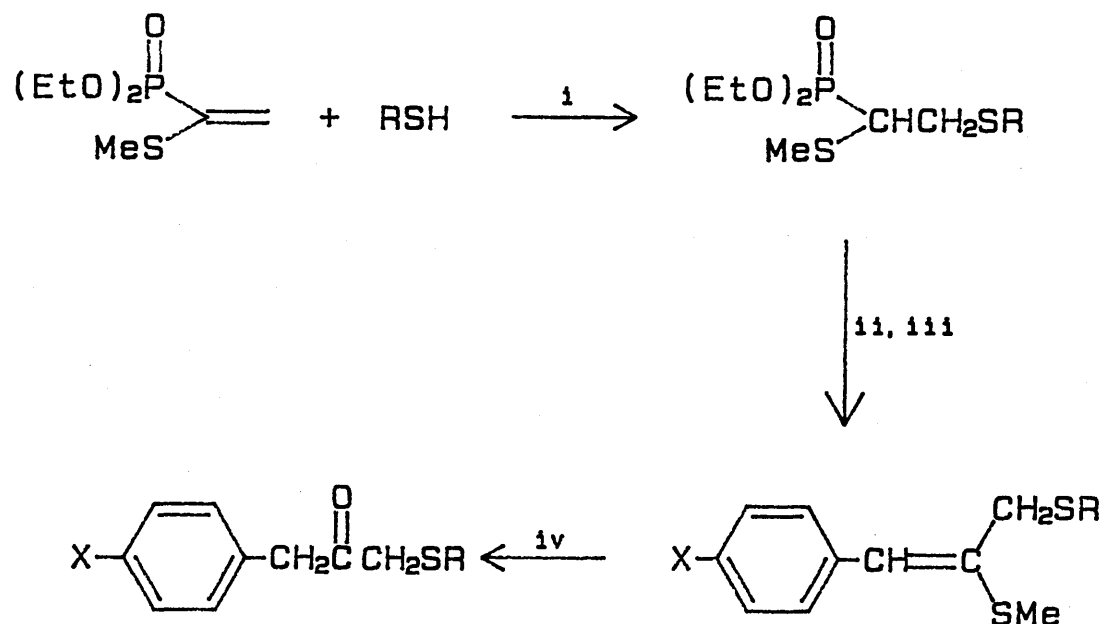


75



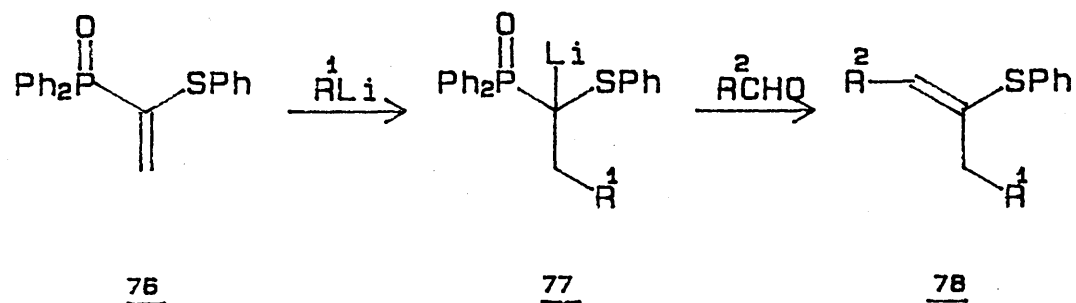
76

variety of nucleophiles⁻ to give carbanions which would then react with aldehydes and ketones to give vinyl sulphides and hence longer chain ketones by alkylative carbonyl transposition:



Reagents: 1, NaOEt, EtOH; 11, NaH; 111, X-C₆H₄-CHO
 iv, TiCl₄, H₂O, CH₃CN

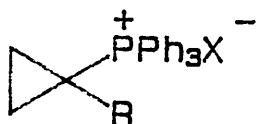
The corresponding phosphine oxide (76) was found to add alkyl lithiums cleanly with MeLi, BuLi and Bu^sLi, but in lower yield with PhLi.^{55(b)} In each case the lithium derivative (77) could be trapped with aldehydes to give moderate yields of the vinyl sulphides (78):



adducts, and so the work was brought to a halt since fuller studies of the better reagents (71c) and (71d) had already been published.

2.3. Wittig reactions utilising cyclopropylphosphonium salts

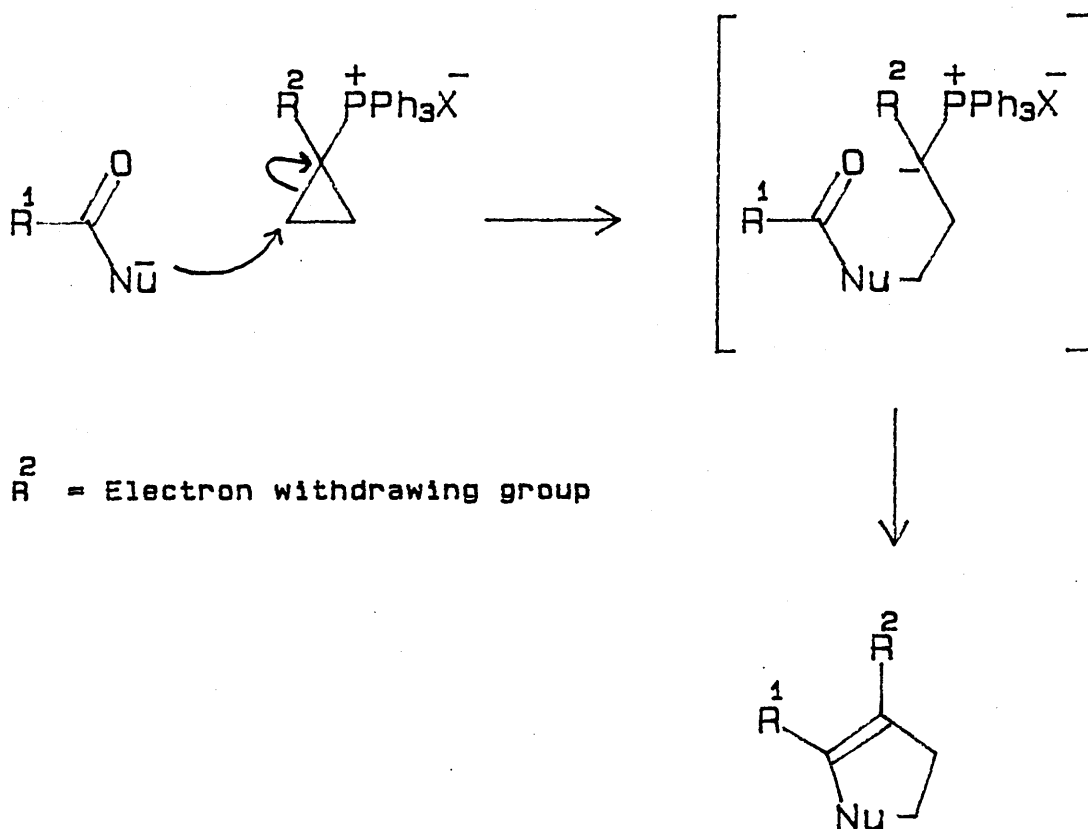
As was shown in the preceding section, a carbonyl compound containing a nucleophilic functional group in a suitable position may be elaborated to a cycloalkene containing two more carbon atoms by reaction with a vinylphosphonium salt (Scheme 4). Three carbon atoms can be introduced by reaction with a cyclopropylphosphonium salt. Schweizer's exploratory studies on cyclopropylphosphonium bromide (79a) demonstrated that this reagent is of limited utility as an annulation reagent ^{56,57} (presumably due to difficulty of the ring opening step).



79

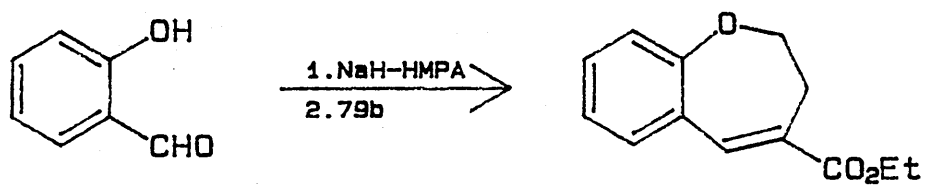
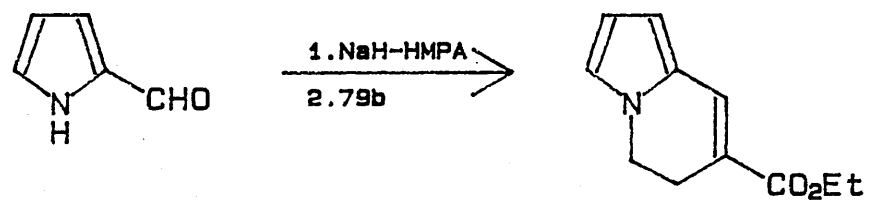
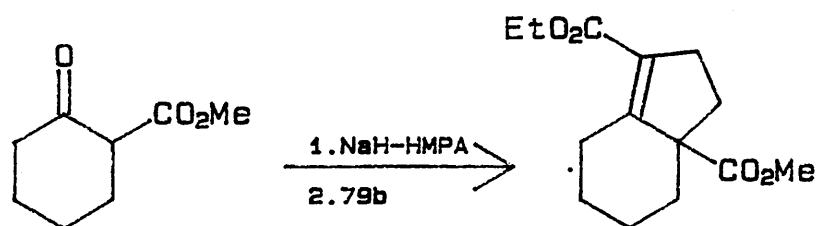
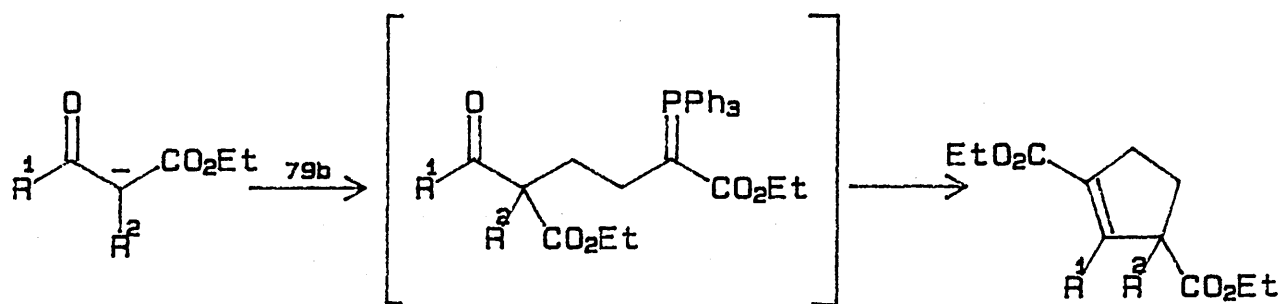
- a R = H , X = Br
- b R = CO₂Et , X = BF₄
- c R = SMe , X = BF₄
- d R = SPh , X = BF₄

additional carbanion-stabilising functional group geminal to the triphenylphosphonium group is necessary in general for a successful intramolecular Wittig reaction (Scheme 7).



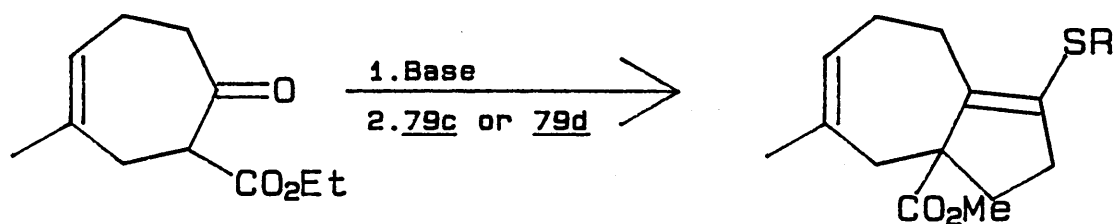
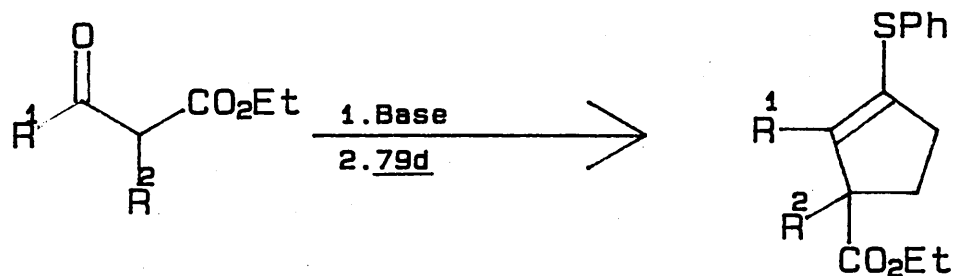
SCHEME 7

In accord with expectations, cyclopropylphosphonium salt (79b), which has a geminal carboethoxy group, proved to be an excellent reagent for the cycloalkenylation of carbonyl compounds.⁵⁸ A few examples are shown below:



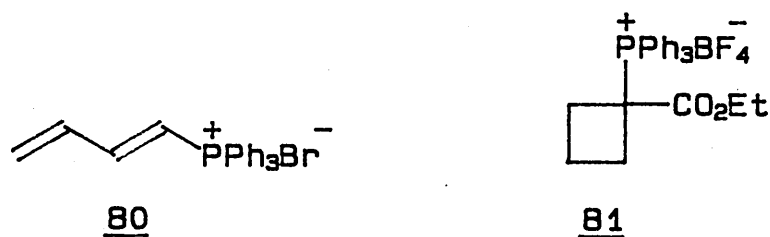
by the alkylthio or arylthio group as shown by Marino.⁵⁹

1-methylthio-and 1-phenylthiocyclopropylphosphonium fluoroborate, (79c) and (79d) respectively have been used in annulation procedures.⁵⁹



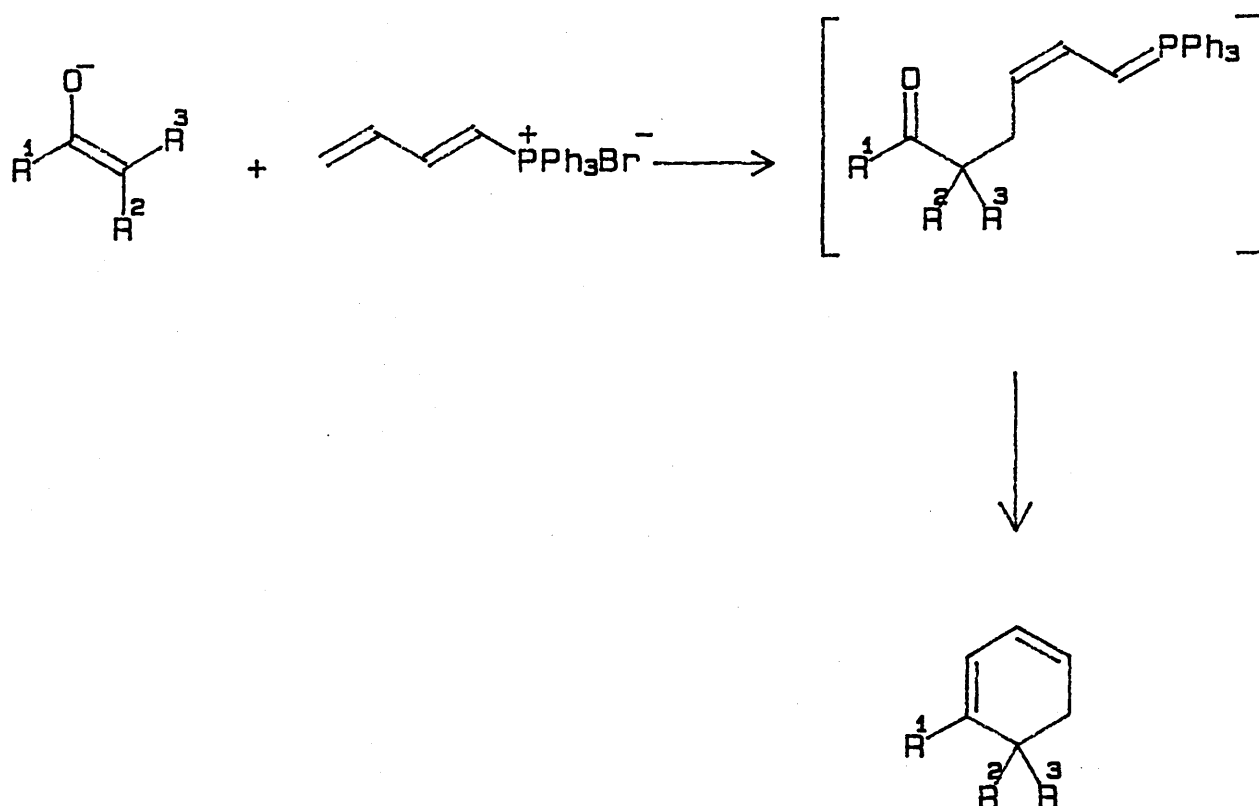
2.4. Wittig reactions utilising Butadienylphosphonium salts

Incorporation of four carbon atoms into a cycloalkene is accomplished by reaction of 1,3-butadien-1-yltriphenylphosphonium bromide (80) with a suitable nucleophile, since 1-ethoxycarbonylcyclobutylphosphonium tetrafluoroborate (81) does not undergo clean ring-opening with nucleophiles.

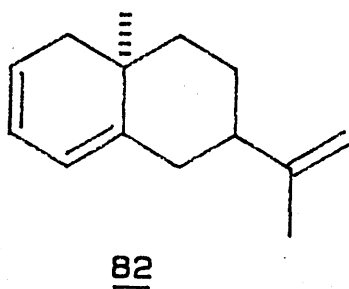


to a propenylidenephosphorane which then cyclises to a

1,3-cyclohexadiene:⁶⁰

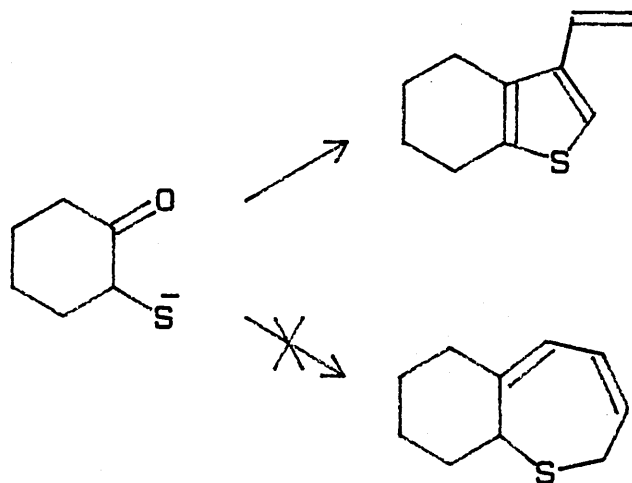


The reaction is fairly versatile and allows the formation of annulated cyclohexadienes such as (82) to be formed.⁶¹

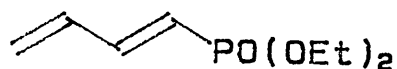


sense that formation of annulated cycloheptadienes was not possible

- instead a five-membered ring was formed:

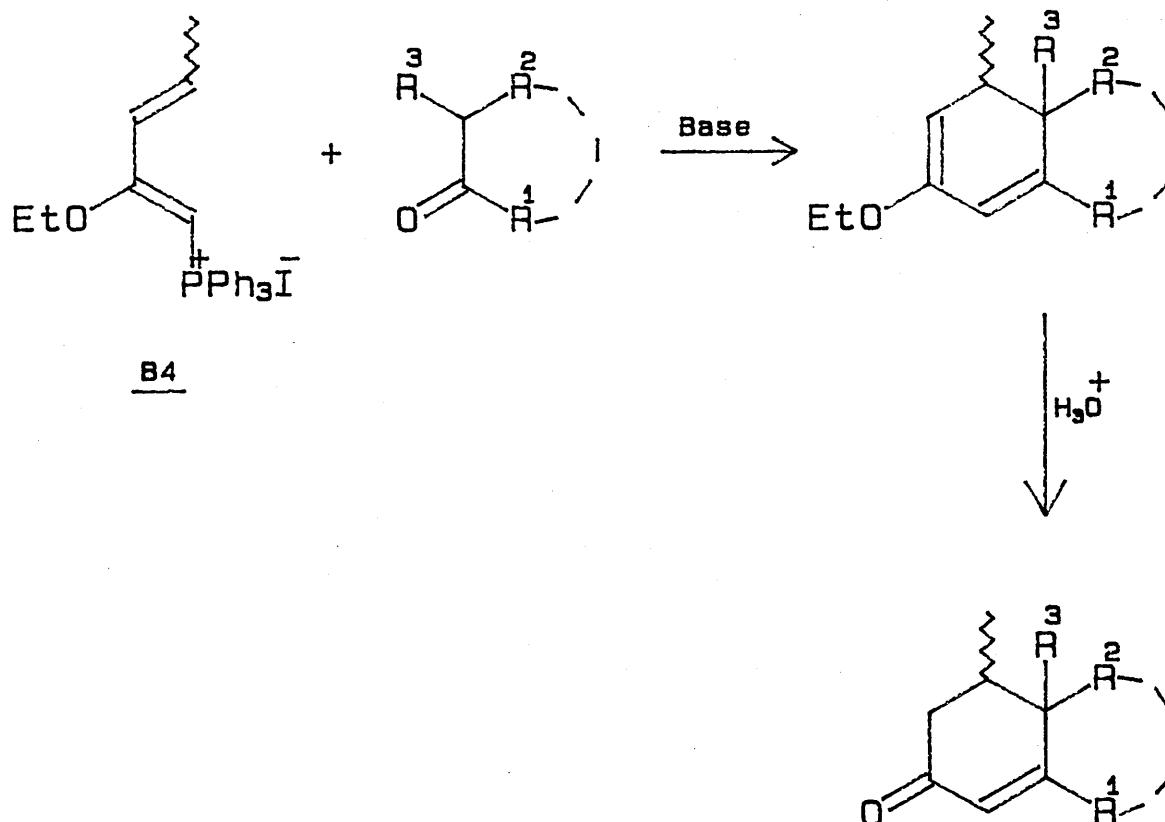


Butadienylphosphonate⁶¹ (83) fails to undergo cyclizations analogous to those of butadienylphosphonium bromide (80). This is not surprising when taking into consideration that phosphonates require an additional electron-withdrawing substituent at the α -carbon atom, if a Wittig-type reaction is to occur.

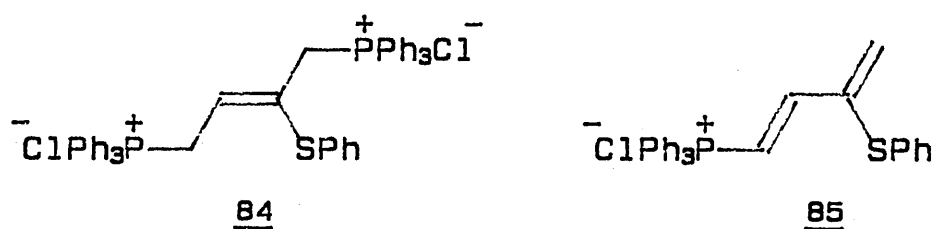


83

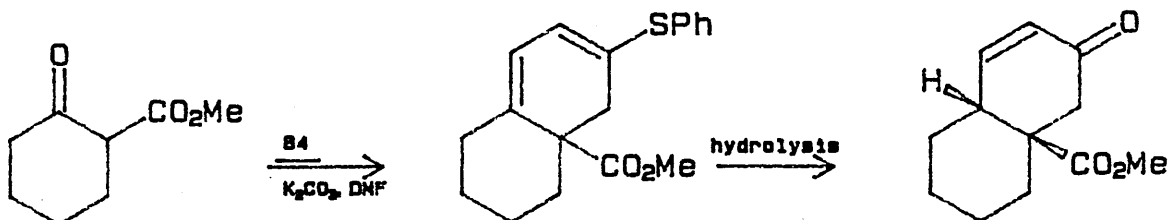
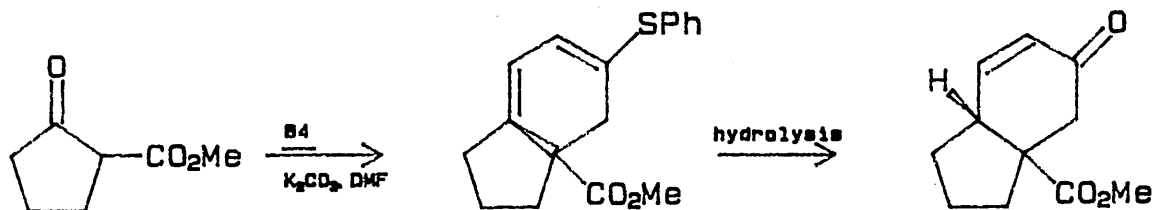
These findings stimulated further studies to ascertain whether other unsaturated, heteroatom-substituted phosphoranes or phosphonium salts might also be useful as synthetic reagents. Martin and Desai⁶² used (2-ethoxy-1,3-pentadienyl) triphenylphosphonium iodide (84) to generate masked enones that were directly hydrolysed to methyl-substituted enones:



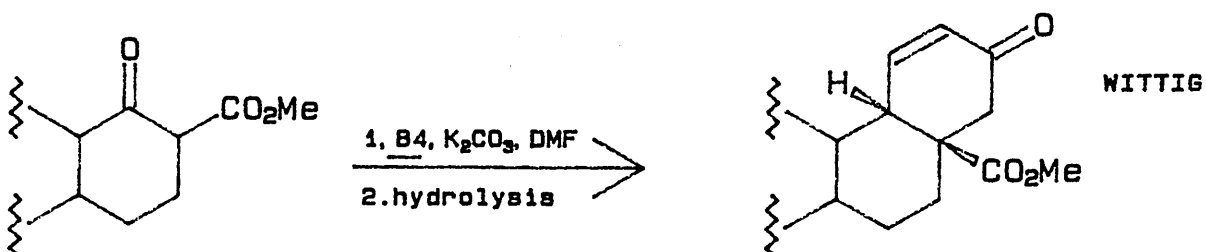
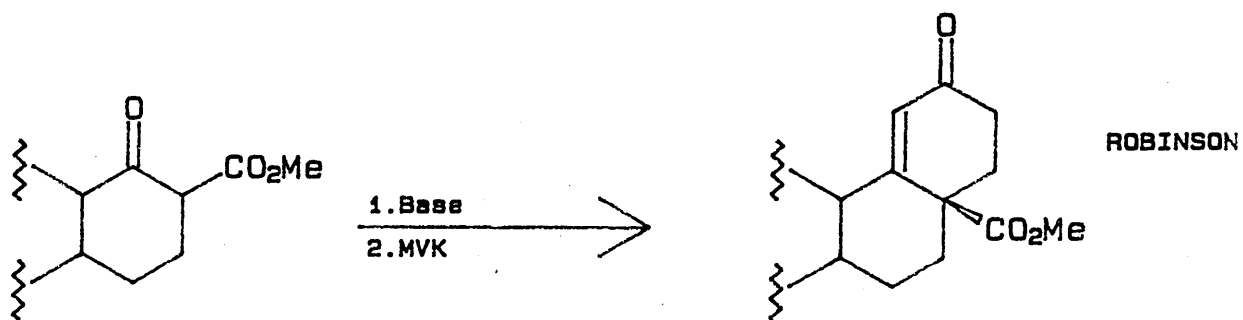
Pariza and Fuchs⁶³ developed a reagent which allows the construction of highly functionalised cyclohexadienes. The bis phosphonium salt (84) is used as a precursor to the dienylphosphonium salt (85).



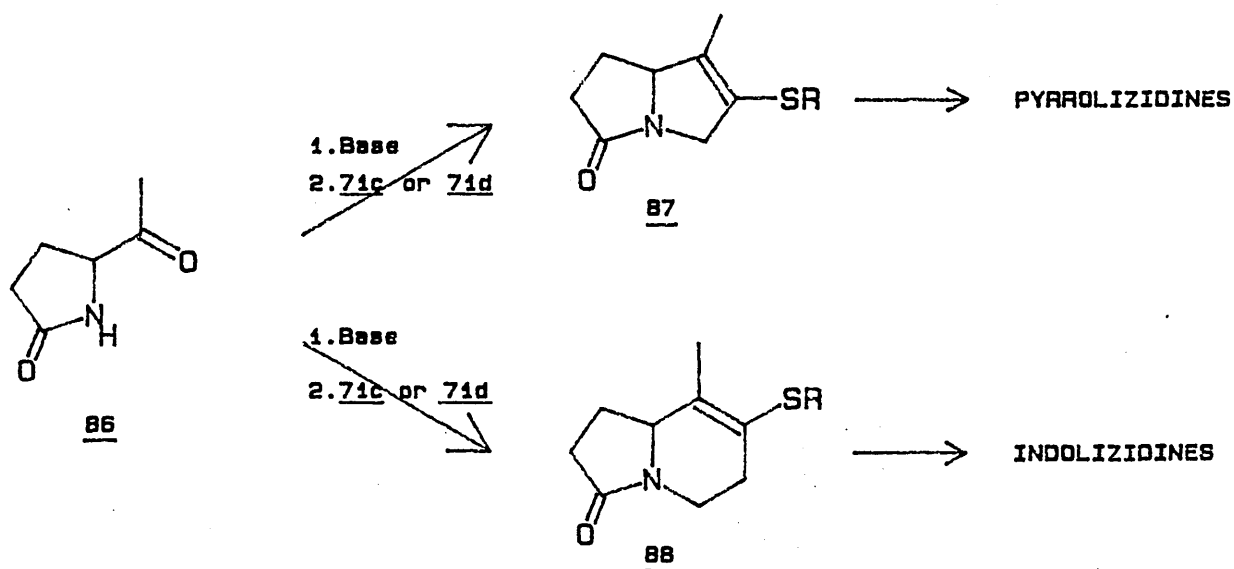
The transient dienylphosphonium intermediate (85) is rapidly attacked by enolates to afford after intramolecular Wittig reaction dienyl sulphides which can then be hydrolysed to enones:



As can be seen their reagent is used to effect a functionalised four-carbon annulation sequence analogous to the well known Robinson annulation, but yielding enones that are transposed relative to the standard regiochemistry:



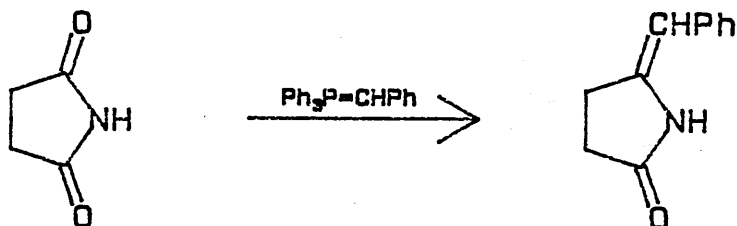
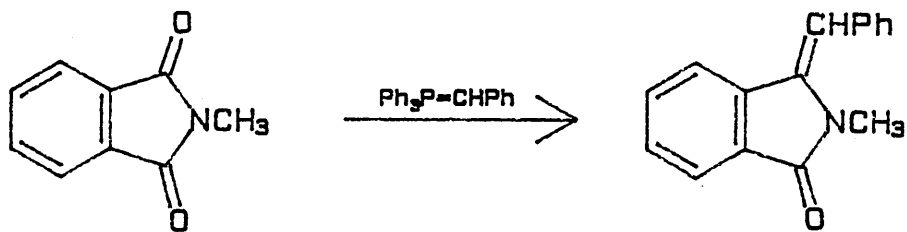
As part of our continued interest in vinylphosphonium salts (71c) and (71d) and their participation in cyclisation reactions, we hope to show their use in the formation of nitrogen bridgehead bicycles which can then be used in pyrrolizidine alkaloid synthesis. In the same way, we also envisage an approach to the synthesis of indolizidine alkaloids using cyclopropylphosphonium salts (79b), (79c) and (79d) (Scheme 8).



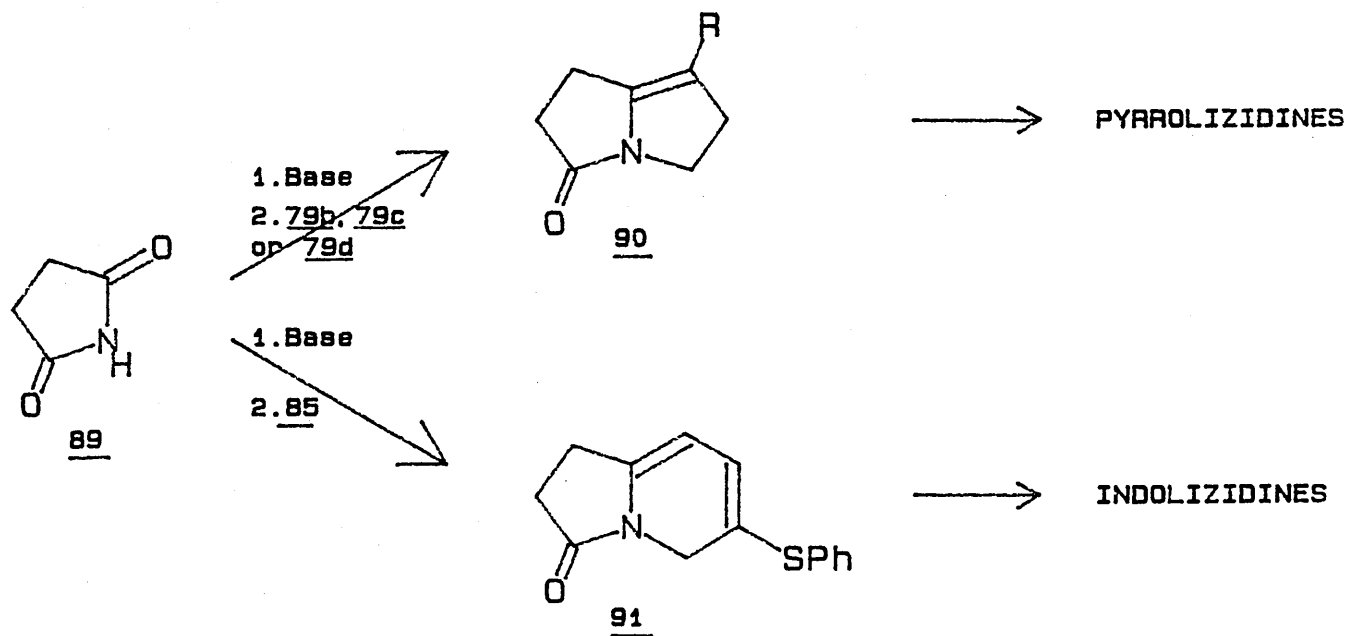
SCHEME 8

The proposed synthetic routes towards pyrrolizidine and indolizidine alkaloids above will be discussed in Chapter 3.

All the Wittig reactions discussed in the previous sections have involved olefination of a ketone carbonyl. It has been shown, however, that imides also undergo reaction with phosphoranes to give products expected of a normal Wittig reaction:⁶⁴



Reaction of succinimide (87) with cyclopropylphosphonium salt (79b), (79c) or (79d) should lead to a functionalised azabicyclic that can be used in pyrrolizidine alkaloid synthesis. Likewise, butadienylphosphonium salt (85) should give access to indolizidine alkaloids (Scheme 9).



SCHEME 9

will be discussed in Chapter 4.

C H A P T E R 3

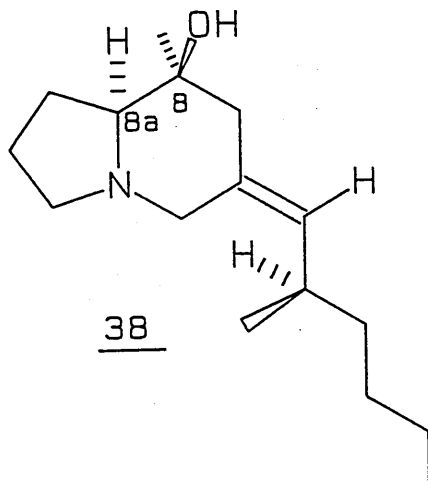
The use of 5-acetylpyrrolidin-2-one in the synthesis of
heterocyclic systems

- 3.1 Introduction
- 3.2 Preparation of 5-acetylpyrrolidin-2-one
- 3.3 Reaction of 5-acetylpyrrolidin-2-one with vinylphosphonium salts
- 3.4 Reaction of 5-acetylpyrrolidin-2-one with vinylphosphine oxides and vinylphosphonate esters
- 3.5 Attempted synthesis of analogues of 5-acetylpyrrolidin-2-one
- 3.6 Reaction of 5-acetylpyrrolidin-2-one with cyclopropylphosphonium salts
- 3.7 Summary and future work.

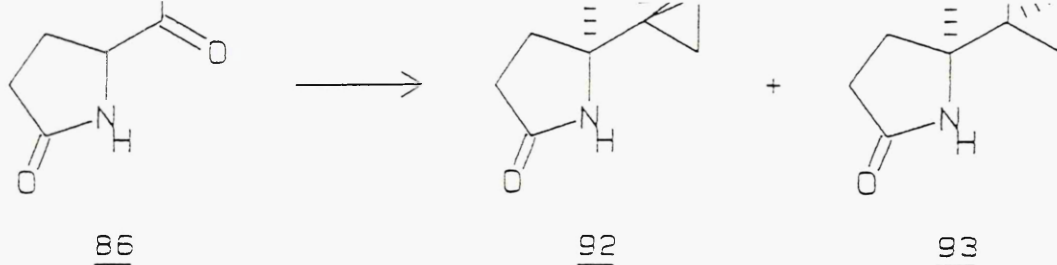
A search of the literature for a compound that could be of use in the formation of nitrogen-bridgehead bicycles led us to 5-acetylpyrrolidin-2-one (86)⁶⁵. We envisaged that the synthesis of such bicycles could be carried out according to Scheme 8 (chapter 2, page 68). 5-acetylpyrrolidin-2-one (86) was chosen as the starting material since its nitrogen atom could act as a nucleophile. Nucleophilic addition of the anion of (86) to vinylphosphonium salts (71c) or (71d) or cyclopropylphosphonium salts (79b), (79c) or (79d), followed by an intramolecular Wittig reaction would give rise to azabicycles (87) and (88) respectively. It was thought that pyrrolizidines would then be accessible from (87) and indolizidines from (88).

3.2. Preparation of 5-acetylpyrrolidin-2-one (86)

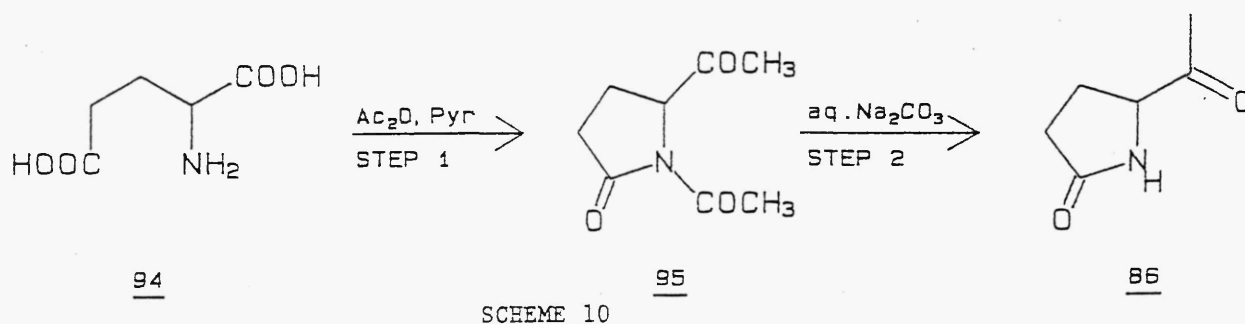
The preparation of (86) was attempted using the method of Thomas et al⁶⁵. Thomas had intended to use (86) in a synthesis of toxin 251D (38).



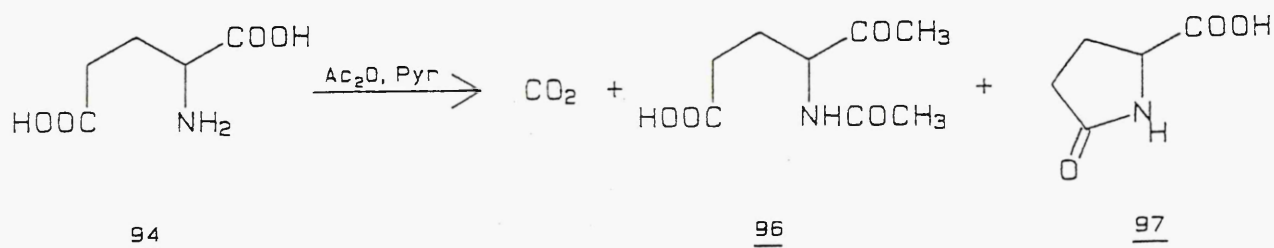
The route to 251D was to involve the epoxide (92) which would establish the required configuration at C-8 and C-8a:



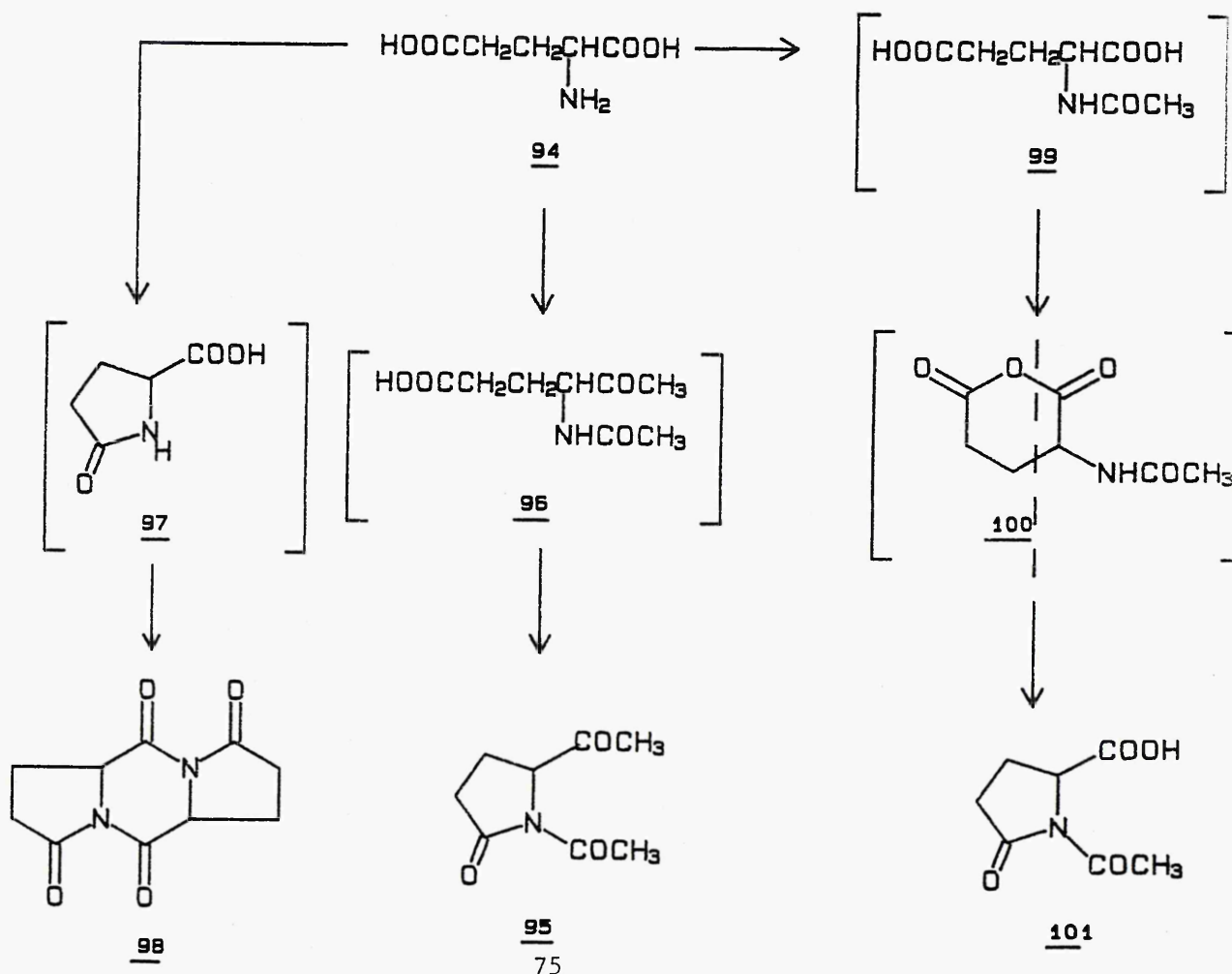
However, in view of Overman's work in this area²⁰ (see chapter 1, Section 1.2.3, page 41) they discontinued the project after reporting the stereoselectivity of the formation of epoxides (92) and (93). The method used by Thomas⁶⁵ for the preparation of racemic 5-acetylpyrrolidin-2-one (86) involved two steps (scheme 10). The initial step was a Dakin-West reaction⁶⁶, involving L-glutamic acid (94), pyridine and acetic anhydride, followed by hydrolysis of the N-acetyl product (95) using aqueous sodium carbonate.



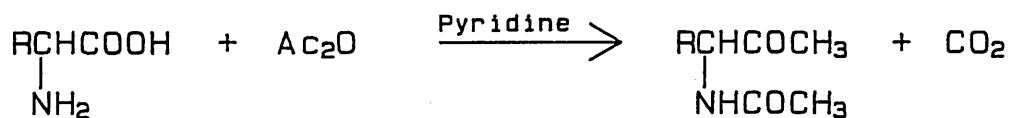
The first step in Scheme 10, that is the reaction of L-glutamic acid (94), pyridine and acetic anhydride, was first reported in 1928 by Dakin and West.⁶⁶ The reaction evolved 15 to 20% of one molecular equivalent of carbon dioxide and so Dakin and West assumed that (96) had been formed (although it wasn't isolated as such). The remainder of the amino acid was assumed to have been converted by the dehydrating action of acetic anhydride to 5-pyrrolidone-2-carboxylic



above reaction in greater detail and had isolated and identified three products. They showed that on treatment with acetic anhydride and pyridine, L-glutamic acid (94) undergoes acylative decarboxylation characteristic of α -amino acids to the extent of 15 to 20%, leading to the acetamidoketo acid (96), which is dehydrated further in the reaction mixture to 1,5-diacetylpyrrolidin-2-one (95). The cessation of the reaction was shown to be partially due, as thought by Dakin and West, to conversion of the glutamic acid to pyrrolidone carboxylic acid (97), but in the reaction mixture this substance is likewise dehydrated, in this case bimolecularly to the tricyclic piperazine derivate (98). The bulk of the starting material is N-acylated to (99) which is internally dehydrated to acetamidoglutaric anhydride (100), and this under the conditions of isolation used by King and McMillan, rearranged to the acetylpyrrolidone carboxylic acid (101), a portion of which may also have been formed in the reaction mixture by direct imidic ring-closure of (99).:

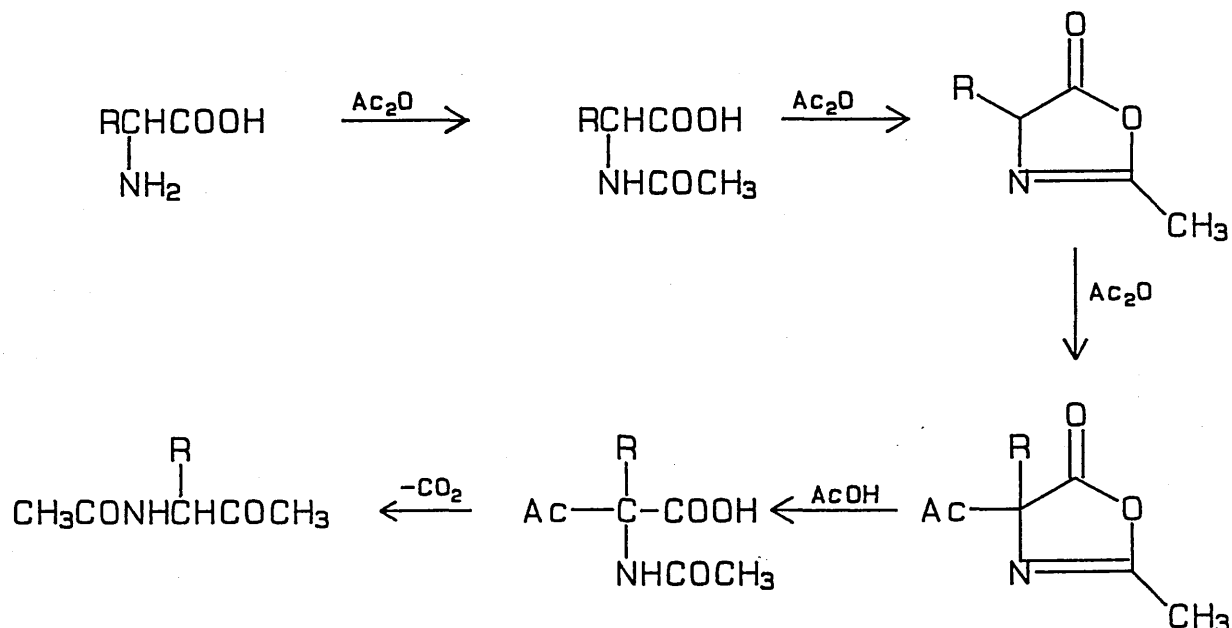


Dakin and West ^{66(b)} had shown that a typical α -amino acid on being warmed with acetic anhydride and pyridine was converted into an α -acetamidoalkyl methyl ketone.



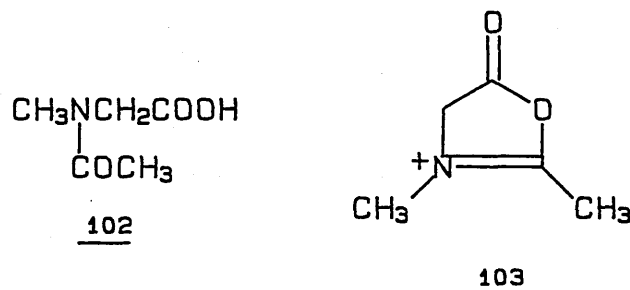
Various mechanisms have been proposed for this reaction and will be discussed briefly.

I. The first type of mechanism, the azlactone mechanism, was proposed by Dakin and West ^{66(a)} and is generally the most favoured one.

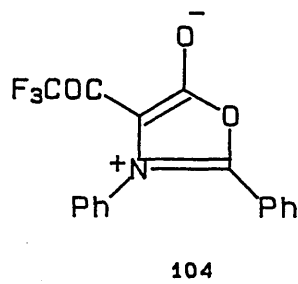


N-acylation of the amino acid is followed by cyclisation to an azlactone. Base catalysed acylation at the reactive 4- position and subsequent conversion of the azlactone to the acetamido ketone and carbon dioxide follows.

amino acids and similar compounds undergo the Dakin-West reaction, for example N-acetyl-sarcosine (102). Several other mechanisms were then put forth in an attempt to explain such reactions. In 1950, Cornforth and Elliot⁶⁸ suggested an oxazolonium cation intermediate (103) to explain the fact that acetylsarcosine (102) underwent the reaction.



Other workers⁶⁹ observed that when N-benzoyl-N-phenylglycine is treated with trifluoroacetic anhydride at room temperature, a mesoionic compound (104) is formed in good yield, which incorporates the trifluoroacetyl group.

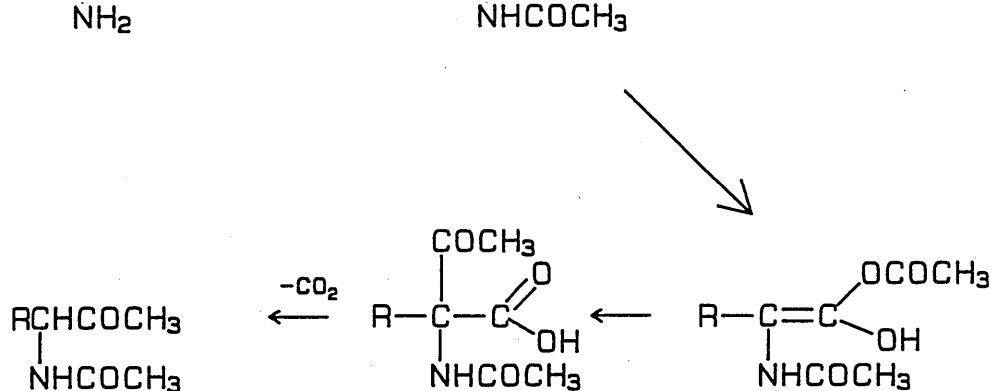


Huisgen and co-workers⁷⁰, also suggested a mechanism involving mesoionic oxazolones.

II The second type of mechanism involves a base-catalysed condensation between two anhydride molecules⁷¹. A cyclic intermediate (105) is involved. The main reason for this proposal was the fact that various assorted compounds other than α -amino acids with primary and secondary amino groups also undergo the same kind of reaction.

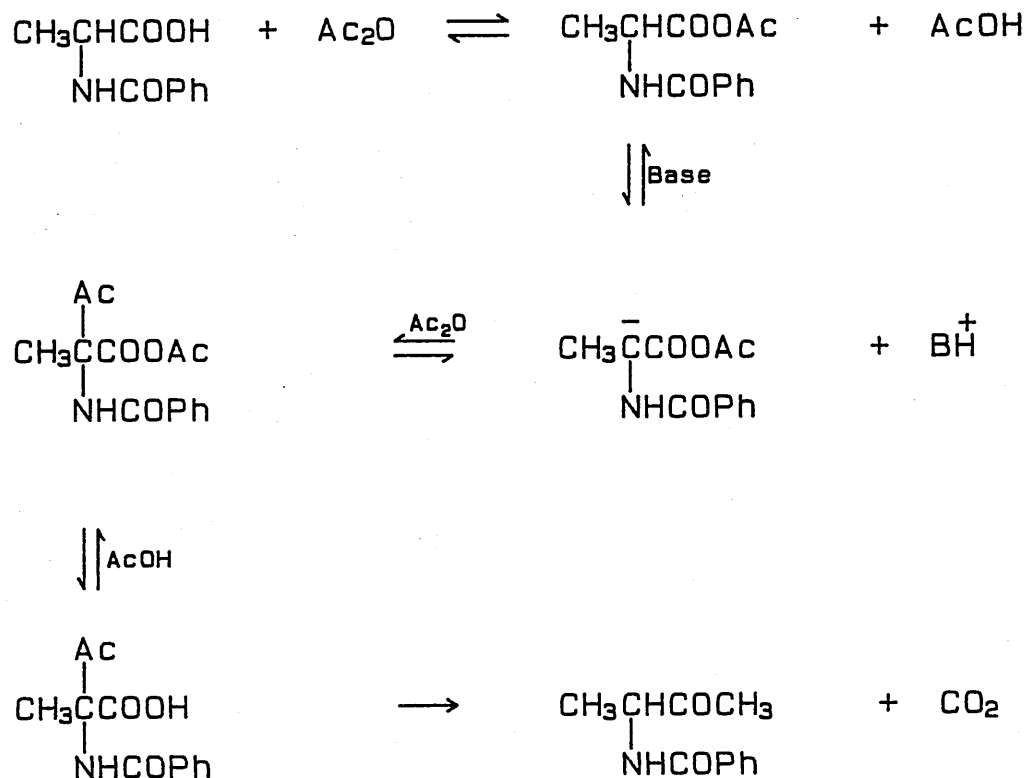


IV A fourth type of mechanism proposed by Levene and Steiger⁷⁴ in 1928 suggested that the amino group and the enol form of the carboxyl group were acetylated. An O→C migration of an acyl group then took place to give the β-keto acid which decarboxylated.



*The formation of a pyridine complex of unknown composition was assumed.

V A fifth type of mechanism is an aldol-type condensation, closely related to the Perkin reaction for the acylative decarboxylation of arylacetic acids. A stepwise mechanism can be written:



most effective in cases where the α -position contained an electron-withdrawing group.

The mechanism was first outlined by Dakin & West⁶⁶ but they soon turned to the azlactone mechanism. The main objection to the simple aldol mechanism carries from the fact that the α -amino group does not directly participate, and it is known that, although other types of acid undergo a similar reaction, the α -amino acids as a class give much better yields of the Dakin-West product.

Allinger and co-workers⁷⁵ carried out some kinetic and mechanistic studies of the Dakin-West Reaction and they concluded that the oxazolone mechanism alone is in accord with the experimental facts under normal conditions.

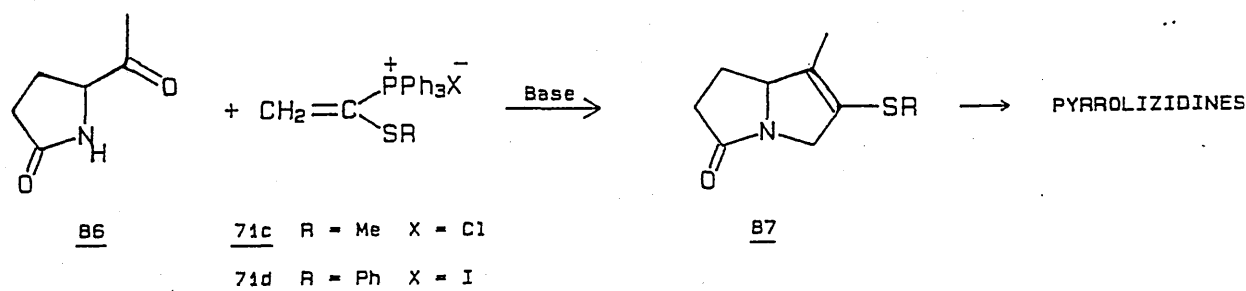
The reaction conditions for the Dakin-West reaction used by King and McMillan⁶⁷ and later by Thomas⁶⁵, involved refluxing L-glutamic acid in pyridine and acetic anhydride for half an hour. The maximum yield of 1,5-diacetylpyrrolidin-2-one (95) they obtained was 29.6%.

Steglich and Hofle⁷⁶ found that 4-dimethylaminopyridine (DMAP) alone or mixed with triethylamine is a superlative acylation catalyst much superior to pyridine, and that in the Dakin-West reaction not only is the acylation accelerated, but the decarboxylative ring fission is also greatly accelerated. Thus, the reaction mixture of L-glutamic acid, acetic anhydride, 4-dimethylaminopyridine and triethylamine, stirred at 60°C for 8 hours, in our hands gave after distillation 78% of the required 1,5-diacetylpyrrolidin-2-one (95).

to the method used by Thomas⁶⁵ for the hydrolysis reaction (Scheme 10, step 2). 1,5-diacetylpyrrolidin-2-one (95) and excess sodium carbonate were dissolved in water and the solution stirred for 5 hours at 20°C. The pH was adjusted to 7 and then the product extracted with dichloromethane using a continuous extraction apparatus for 25 hours. 5-acetylpyrrolidin-2-one (86) was obtained as an off-white solid in 73% yield.

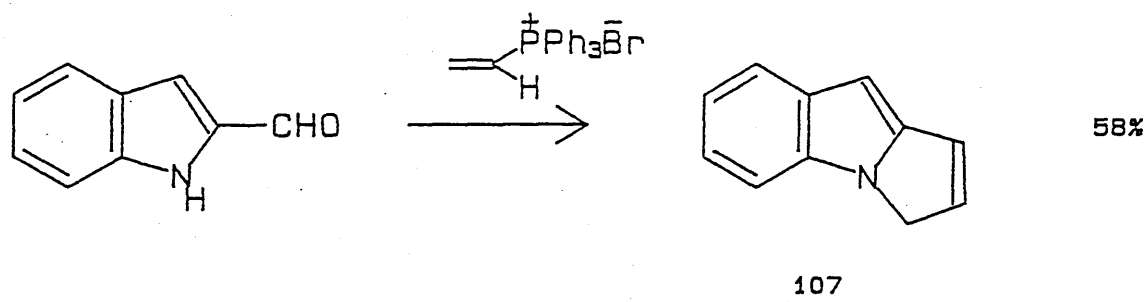
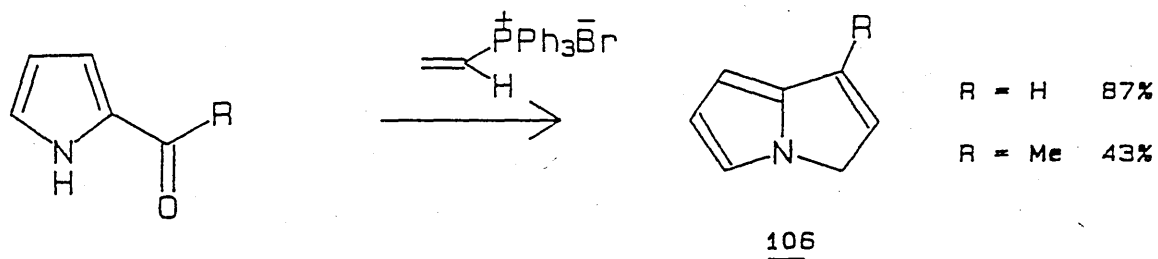
3.3. Reaction of 5-acetylpyrrolidin-2-one with vinylphosphonium salts

We describe in this section the use of 5-acetylpyrrolidin-2-one (86) and vinylphosphonium salts (71c) and (71d) in an approach to the synthesis of pyrrolizidines (87).

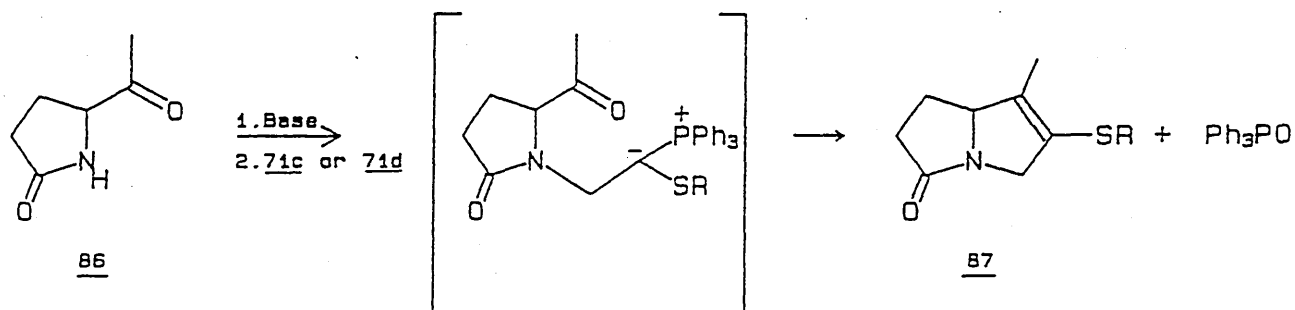


We were encouraged by some earlier work by Schweizer⁷⁷ on the synthesis of pyrrolizines (106) from 2-acylpyrroles, and pyrroloindole (107) from 2-formylindole.

Schweizer's work, however, leads to the formation of unsymmetrical alkenes which limits their use in the synthesis of complex organic molecules. Our approach to pyrrolizidines involves the formation of a heterocyclic compound containing a vinyl sulphide which is susceptible to a number of synthetic transformations.



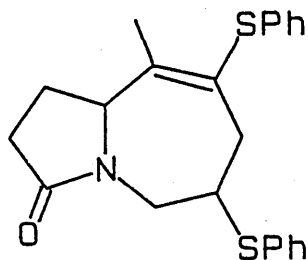
Previous work in our laboratories on the use of vinylphosphonium salts (71c) and (71d) in intramolecular Wittig reactions has shown that the reaction proceeds cleanly, and with good yields of the expected product under mild conditions ⁴⁵⁻⁵³. From this starting point it was anticipated that 5-acetylpyrrolidin-2-one (86) should react with (71c) and (71d) as shown in Scheme 11.



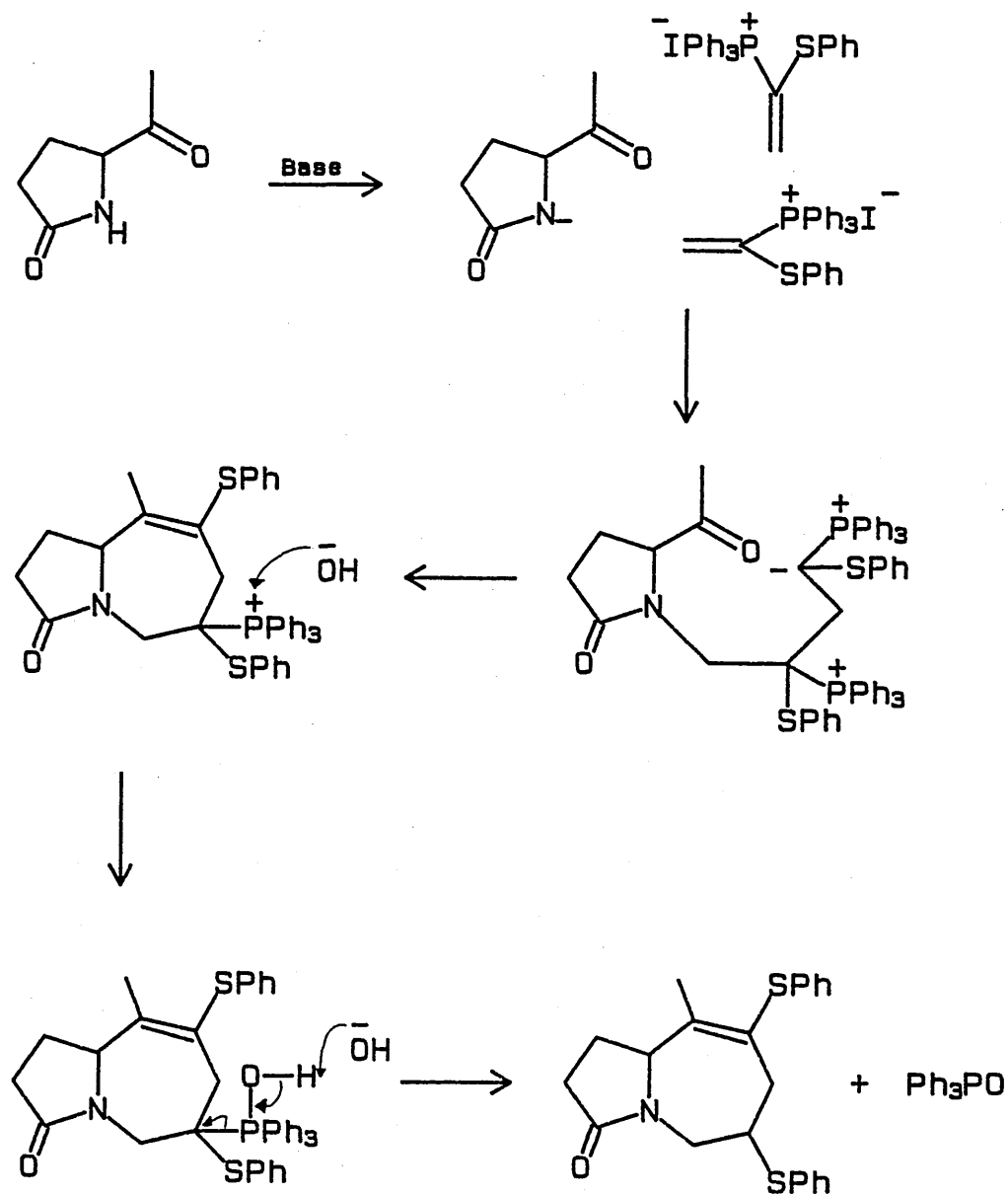
SCHEME 11

tetrahydrofuran (THF) for 15 minutes at room temperature gave the sodium salt as a pale yellow solid. Vinylphosphonium salt (7ld) was then added and the mixture refluxed for 5 hours. There appeared to be one major plus several minor products formed in the reaction mixture (TLC evidence). We were disappointed to find, however, that the major product had the same R_f value as triphenylphosphine oxide, the Wittig by - product. Treatment of the TLC plate with the spray reagent iodoplatinic acid (IPA), showed the major product as a spot which showed both purple and yellow areas suggesting the presence of two compounds. Comparison with a test sample of pure triphenylphosphine oxide was encouraging since this gave only a purple spot.

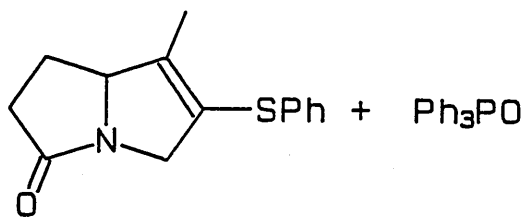
On work-up the first product to be eluted during short column chromatography gave a proton nmr spectrum similar to that expected of the product (87); that is a singlet at 7.23 δ (Ph), multiplets in the region 4 - 4.7 δ and 3.3 - 3.8 δ (CH next to alkene), a multiplet at 1.8 - 3.0 δ (CH₂ manifold) and a singlet at 1.8 δ (CH₃). The proton integration, however, inferred that double the amount of expected phenyl groups were present. Mass spectrometry and micro-analysis proved this compound to be a 5/7 fused bicycle:



3% yield. We were not surprised however at its formation since we worked with two equivalents of vinylphosphonium salt (71d) and Posner⁴² had already demonstrated a similar reaction (see Chapter 2, section 2.2., page 54). In our situation the anion of 5-acetylpyrrolidin-2-one (86) underwent a Michael - Michael ring - closure annulation reaction to form the 5/7 fused bicyclic product as follows:



gave a proton nmr that appeared to indicate a mixture of the desired product (87, R=Ph) and triphenylphosphine oxide.



Peaks occurred in the spectra at 7.70 δ (6H) and 7.25 - 7.62 δ (9H) which were typical of triphenylphosphine oxide. The peaks that were thought to be due to the product occurred as follows:

A singlet at 7.15 δ that integrated for 5 protons (SPh).

Multiplets at 4.05 to 4.76 δ and 3.30 to 3.80 δ that integrated for a total of 3 protons (NCH₂ and NCH).

Multiplet at 1.93 - 3.0 δ that integrated for 4 protons (CH₂CH₂).

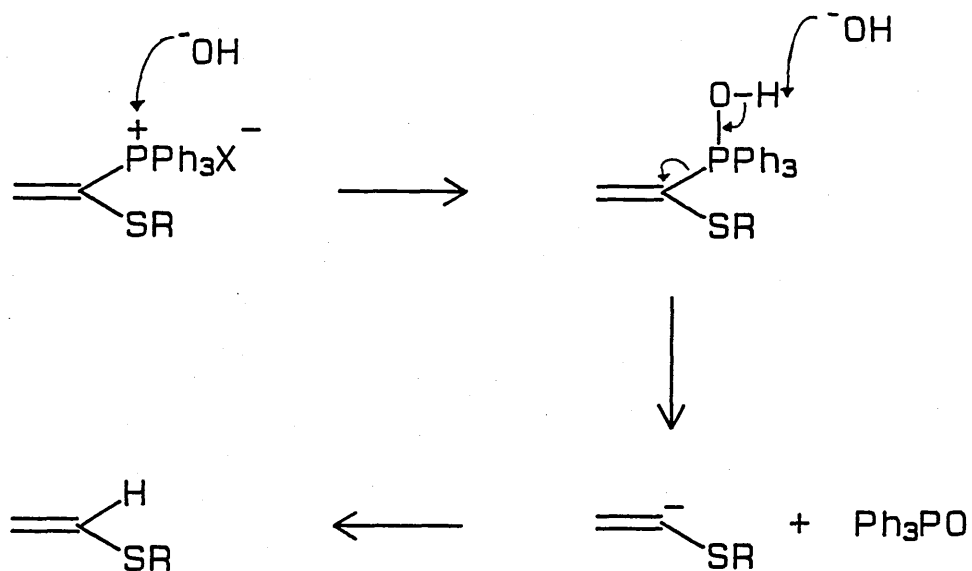
Multiplet at 1.8 δ that integrated for 3 protons (CH₃).

oxide was subjected to a full GC|MS scan using a 1.25% Dexsil 300 column with a 260°C isothermal and 250°C inlet. Analysis by mass spectrometry of the more volatile component showed the base peak at 245 which corresponded to the molecular ion. Study of the fragmentation pattern permitted identification of the parent molecule as (87d). For example:

<u>Observed peaks</u>	<u>Fragment(s) lost</u>
245 (molecular ion)	
230	- CH ₃
189	- $\begin{array}{c} \text{O} \\ \\ \text{CCH}_2\text{CH}_2- \end{array}$
136	- SPh
121	- CH ₃ and - SPh
55	- CH ₂ CH ₂ - and $\begin{array}{c} \text{CH}_3\text{SPh} \\ \\ \text{C}=\text{C}-\text{CH}_2- \end{array}$

The less volatile species was identified as triphenylphosphine oxide. Thus both NMR and GC/MS results confirmed the mixture to be compound (87d) and triphenylphosphine oxide.

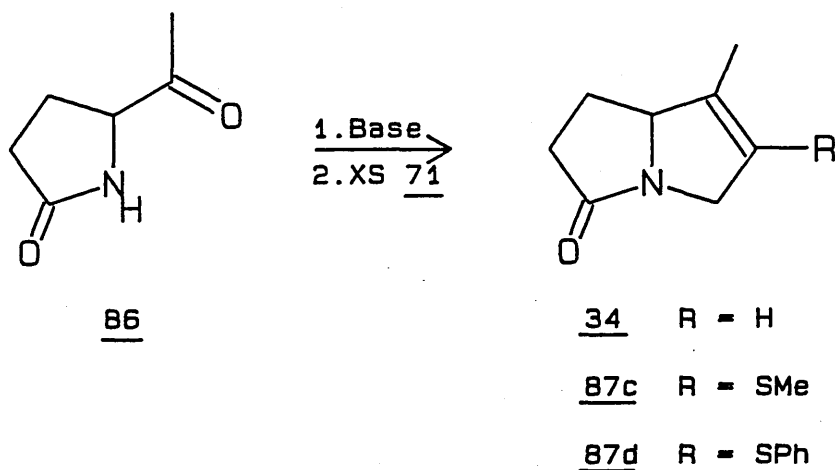
from the GC peak areas and also from the NMR integration. Initially the ratio of product (87, R=Ph) to triphenylphosphine oxide was low; this was thought to be due to hydrolysis of the vinylphosphonium salt (71d) in the reaction mixture:



Since, as already stated, we were working with an excess of the vinylphosphonium salt (71d), the triphenylphosphine oxide produced could have arisen not only as a Wittig reaction by-product but also from hydrolysis of (71d).

However, after a number of attempts, ensuring all reagents and glassware were thoroughly dry, the ratio and yield were improved.

work using different vinylphosphonium salts:



<u>Phosphonium</u>	<u>Reaction</u>	<u>Product</u>	<u>Product : Ph₃PO</u>	<u>Calculated</u>
<u>Salt</u>	<u>Conditions</u>		<u>Ratio</u>	<u>Yield of Product</u>
71a	reflux/60hr	34a	1 : 1.7 (NMR)	25%
71c	reflux	87c	1 : 1,5 (NMR)	27%
71d	reflux/5h	87d	1 : 1.8 (NMR,GC/MS)	58%

TABLE 1

NOTE

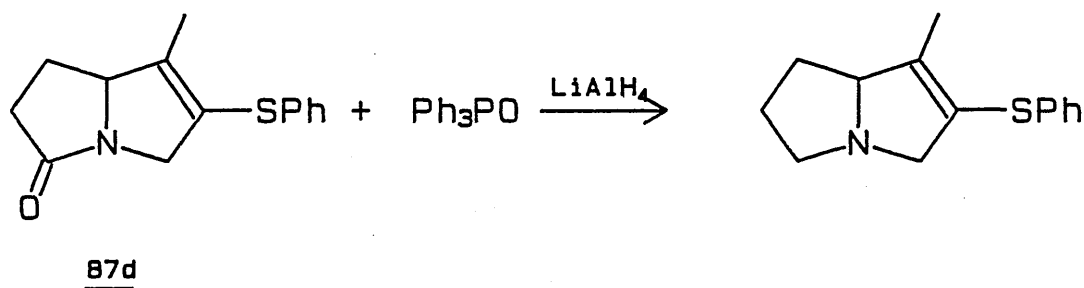
The reaction with vinylphosphonium salt (71c) was a once only attempt. No doubt the yield and ratio could have been improved with successive attempts.

The above demonstrates the better yields of intramolecular Wittig product (87) achieved with our vinylphosphonium salts (71c) and (71d).

separation of the Wittig by-product Ph_3PO , and the bicycle (87).

We concentrated our efforts in this area on azabicyclo (87d), since this was formed in the greatest yield (see Table 1). Chromatographic separation of (87d) and Ph_3PO on silica gel could not be achieved and large scale gas chromatographic separation was not feasible. We therefore had to explore the possibility of separation by other means.

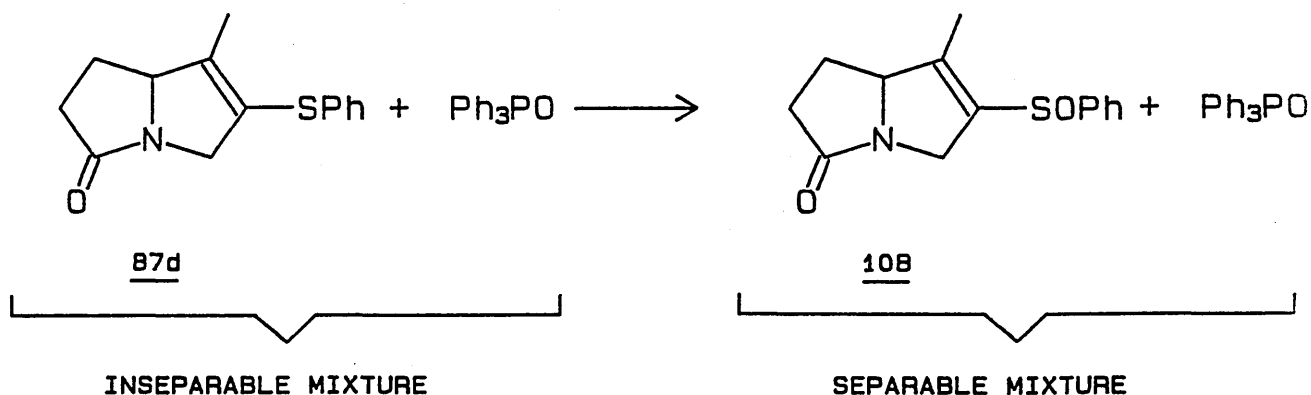
An attempt to separate the mixture by lithium aluminium hydride reduction was carried out but was unsuccessful.



It was thought that reduction of the mixture would give the above pyrrolizidine which would allow for separation from triphenylphosphine oxide. The product formed was more polar than the starting materials. After work-up spectral analysis showed that the expected product had not been formed.

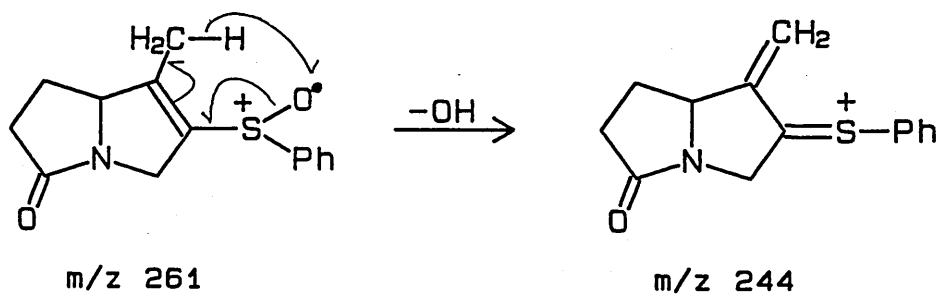
It was thought that oxidation might be a possible solution to the problem of separation since it is known that sulfoxides are more polar than sulphides. Thus the product mixture of (87d) and triphenylphosphine oxide was dissolved in dichloromethane/tetrahydrofuran, cooled to -78°C and metachloroperbenzoic acid (mcpba) added. On work-up it was seen that two products were present (TLC evidence). Separation using short column chromatography gave sulfoxide (108) and a mixture of triphenylphosphine oxide and

later confirmed by the oxidation of a pure sample of (87d). (See section 3.4 for the preparation of pure (87d).



The proton NMR spectrum of sulfoxide (108) was similar to that of sulfide (87d) except the peaks due to SPh and CH_3 were shifted slightly downfield.

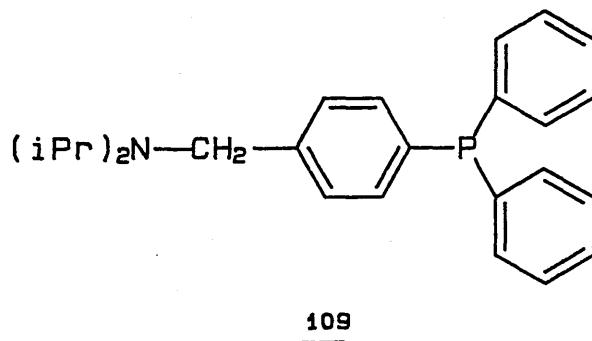
The mass spectrum of sulfoxide (108) showed peaks at m/z 261 and 244 which is a good example of the ortho-effect:



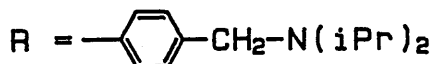
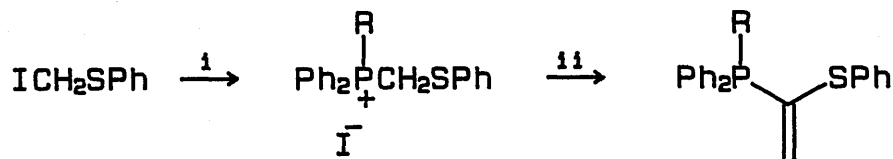
The other main peaks occurred at m/z 135 (loss of $-\text{OH}$ and $-\text{SPh}$) and m/z 55 (loss of $-\text{CH}_2\text{CH}_2-$ and $-\text{C}(\text{CH}_3) = \text{C}(\text{SOPh}) - \text{CH}_2-$)

Although oxidation of the reaction mixture was a solution to the separation problem, it was felt that a one-step preparation of (87d) via a Wittig reaction should be possible. We therefore turned our attentions to forming an acid soluble vinylphosphonium salt.

a simple derivative of triphenylphosphine which possessed a highly hindered amine function that allowed for easy aqueous acid extraction of the phosphine oxide by-product from the Wittig reaction mixture. He suggested that reagent (109), a viscous oil could be substituted for triphenylphosphine in the Wittig reaction.

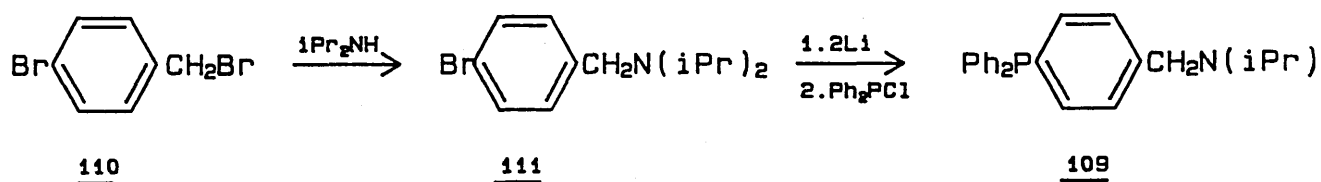


We therefore anticipated that reagent (109) could be used in the formation of a new vinylphosphonium salt. Our envisaged synthetic route involved the same procedure as that used in the preparation of vinylphosphonium salts (71c) and (71d) (see scheme 5, chapter 2, page 56) the exception being that the triphenylphosphine would be replaced by reagent (109):



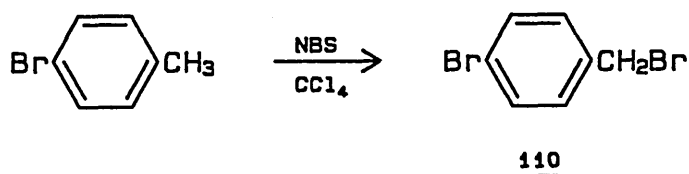
Reagents: (i) 109/CH₃CN/reflux (ii) CH₂=N⁺(CH₃)₂Cl⁻/CH₃CN/reflux

was carried out by Bottaro as follows:



Our attempts at this preparation, however, showed that the final step was not without difficulties.

Although 4-bromobenzylbromide (110) is available commercially we found it could be made in 60% yield by refluxing 4-bromotoluene and N-bromosuccinimide (NBS) in carbon tetrachloride for 90 hours. A few crystals of benzoyl peroxide were added to the reaction mixture to initiate the reaction.



The progress of the reaction was monitored using ¹H nmr. A disappearance of the singlet at 2.35δ and formation of a singlet at 4.50δ was observed.

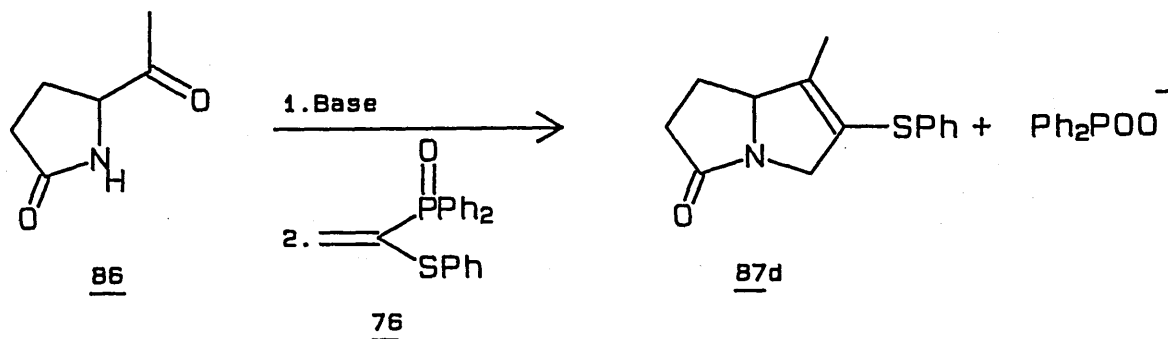
The synthesis of 4-bromobenzyl-diisopropylamine (111) was carried out by refluxing 4-bromobenzylbromide (110) in diisopropylamine.

Methyl iodide was added as a catalyst and it was found that the yield of product could be increased by increasing the reaction time. Yields of 92% were eventually achieved with a 4 day reflux.

diisopropylamine (111) to a suspension of lithium in ether/THF (80/20) under an atmosphere of nitrogen. After addition, the reaction mixture was refluxed for 2 hours. Chlorodiphenylphosphine was then added dropwise and the reaction mixture refluxed for one hour. This final step was carried out several times and it was disappointing to find that the expected product could not be obtained. We decided not to pursue this route any further since at that time we were also investigating the preparation of a vinylphosphine oxide which later proved to offset a solution to the problem we were experiencing in our Wittig reaction. (See section 3.4. below).

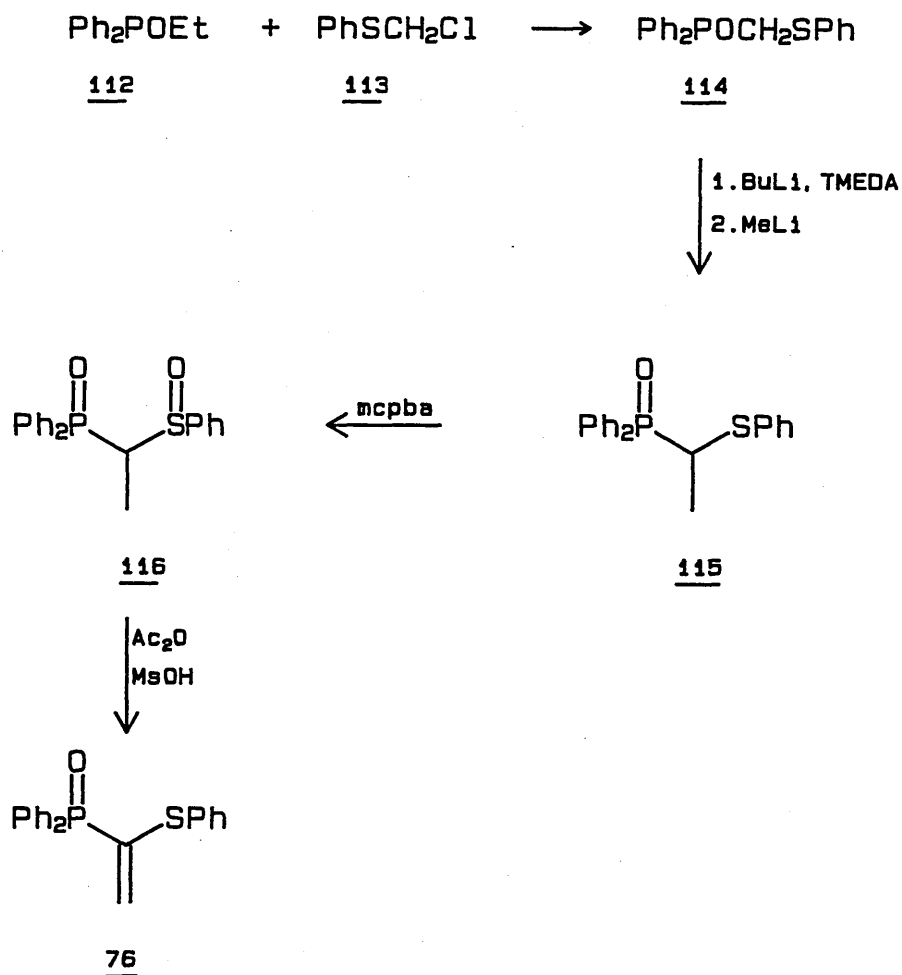
3.4. Reaction of 5-acetylpyrrolidin-2-one with vinylphosphine oxides and vinylphosphonate esters

The major problem with our Wittig reaction was separation of the alkene (87) from triphenylphosphine oxide. However, as described in Chapter 2, PO activated olefin synthesis is a useful supplement to the Wittig reaction, one of the main advantages being separation of the products. Since Warren⁵⁵ had already described the synthesis of 1-phenylthiovinyl-diphenylphosphine oxide (76) it was anticipated that product (87d) should be readily available from the reaction of 5-acetylpyrrolidin-2-one (86) with (76).



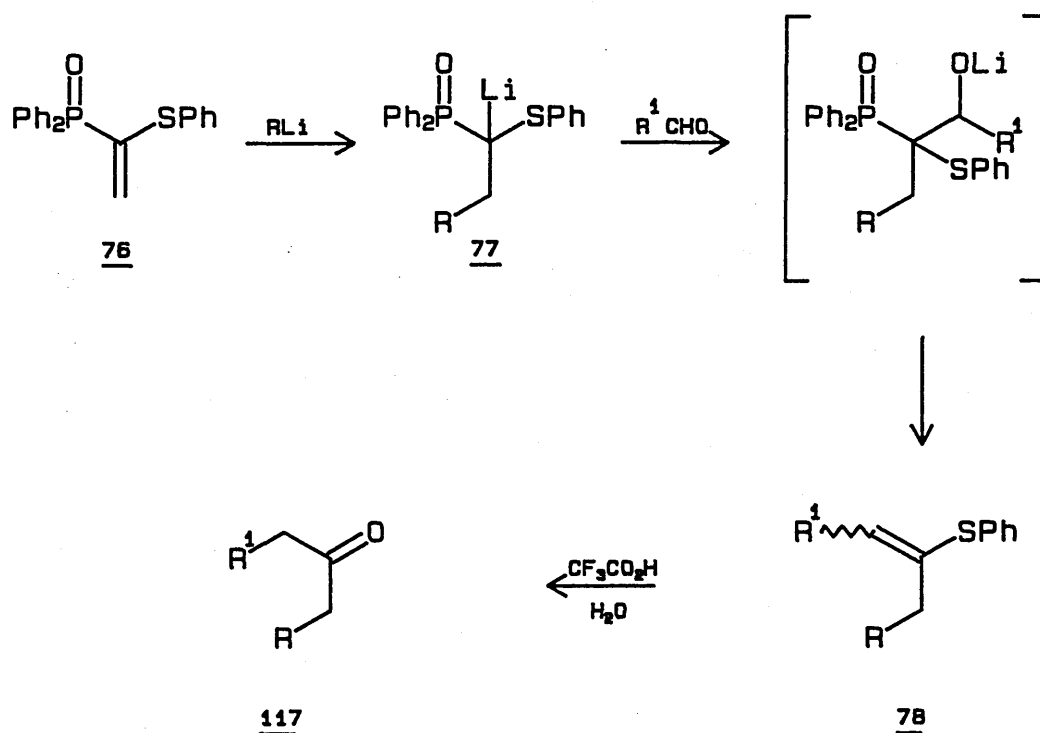
the above reaction would be water soluble making separation from the azabicycle (87d) very simple.

The preparation of (76) was carried out as follows:



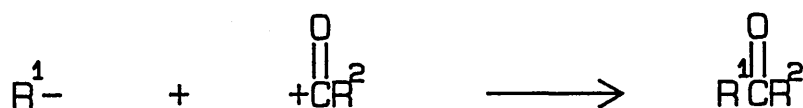
An Arbuzov reaction between ethoxy diphenylphosphine (112)⁸⁰ and chloromethyl phenyl sulphide (113)⁸¹ gave good yields of diphenyl(phenylthiomethyl) phosphine oxide (114)⁸². The substituted compound (115) was made by methylation of the anion of (114)⁸². The ability of sulphur to transfer functionality to an adjacent carbon atom is the basis for the next step. Oxidation of (115) gave a mixture of sulfoxides (116)⁵⁵. The Pummerer elimination procedure, in which the sulfoxides are acetylated under acid conditions, gave a good yield of (76)⁵⁵ but required 8 days at room temperature.

involved addition of an alkyl lithium to (76) to produce the anion (77). Quenching of this anion with an aldehyde gave vinyl sulphide (78) in one step from (76) since the electron-withdrawing PhS group accelerates the elimination of $\text{Ph}_2\text{P}^-\text{O}^-$.

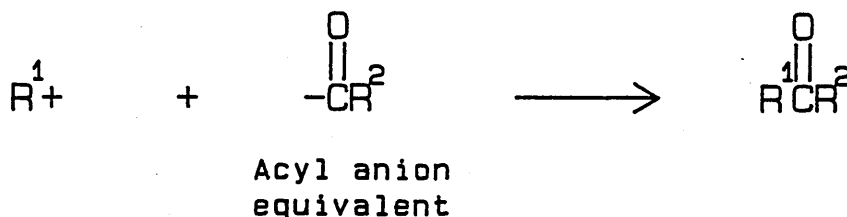


The vinyl sulphides (78) were formed as mixtures of geometrical isomers, both giving the same ketone (117) on hydrolysis in trifluoroacetic acid.

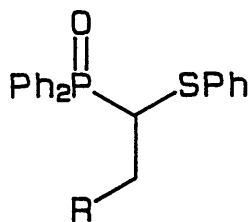
Consideration of the above ketone formation shows it is totally opposite to conventional ketone synthesis. Conventional ketone synthesis involves the addition of a carbon nucleophile to a carbon electrophile, the electrophilic carbon atom becoming the new carbonyl carbon.



from the nucleophilic carbon of an acyl anion equivalent:



Warren⁵⁵ stated that although trapping of the lithium derivative (77) with aldehydes gave moderate yields of the vinyl sulphides (78), addition of (77) to ketones gave none of the corresponding adducts - proton transfer occurred instead and (118) was isolated.

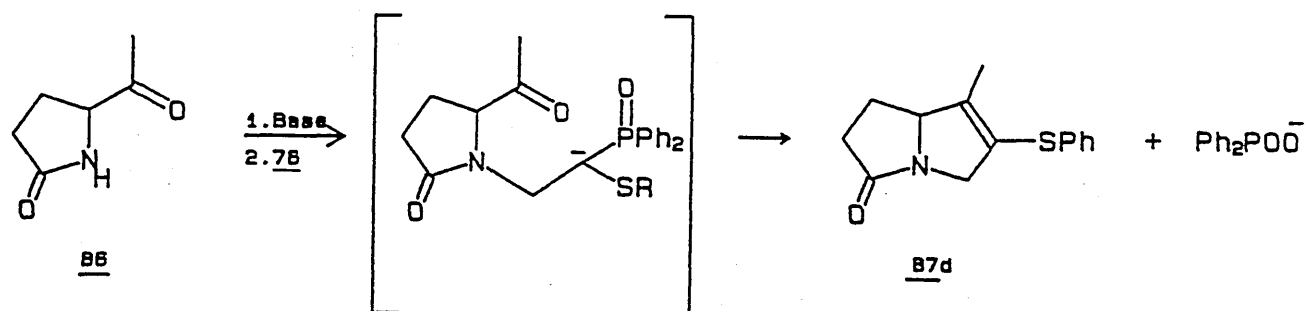


118

This lack of reactivity with ketones in the Wittig reaction is one of the problems with phosphorus containing acyl anion equivalents: Presumably the extra stability given to the anion (77) by the sulphur atom allows the sterically favourable abstraction of an α -proton to be the major reaction.

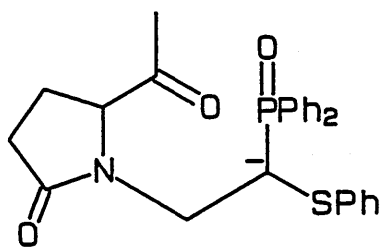
Warren^{55b} brought his work on vinylphosphine oxide (76) to a halt due to the publication of Hewson's and Mikolajczyk's much fuller studies of what he regarded as the better reagents (71c) and (71d)^{45,46,48-53} and (75)⁵⁴.

(71d) indicated that vinylphosphine oxide (76) should be a suitable substitute for (71d) in the reaction:



Treatment of the anion of (86) in THF with vinylphosphine oxide (76), followed by refluxing for 2 hours gave 71% of (87d). Proton nmr and mass spectral details were identical to those obtained for the analogous vinylphosphonium salt reaction, except in this case the peaks due to triphenylphosphine oxide were absent in the ^1H nmr spectra. The fact that compound (87d) had been produced from 5-acetylpyrrolidin-2-one using two different precursors helps to confirm its presence.

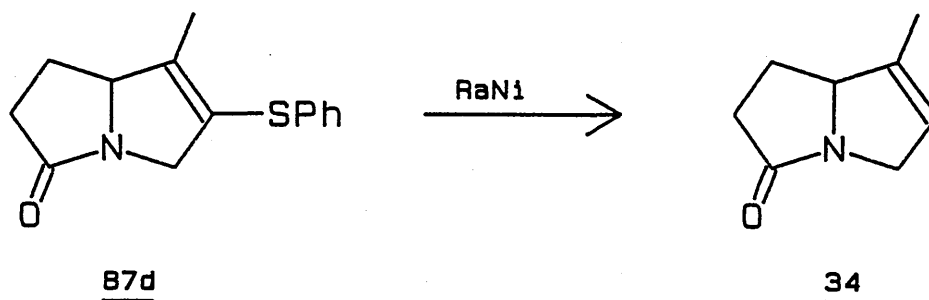
vinylphosphine oxide (76) with 5-acetylpyrrolidin-2-one (86)
 backs-up Warrens⁸² general statement that : "for most applications
 in synthesis, the diphenylphosphinoyl (Ph_2PO) group is superior to
 the triphenylphosphonium (Ph_3P^+) in that the reagents are usually
 crystalline, reactivity and yields are higher, and separation of the
 Wittig by-product, diphenylphosphinic acid, is very simple." Our
 results, however, contradict Warren⁵⁵ in that he found that
 vinylphosphine oxide (76) would not react with ketones; in our case,
 (76) reacted with ketone (86) under mild conditions to give good
 yields of the expected product. The difference between our work
 and Warrens work utilising vinylphosphine oxide (76)⁵⁵ is that
 Warren was attempting intermolecular Wittig reactions whereas we
 were involved in intramolecular Wittig reactions. Warren formed
 the anion (77) by addition of an alkyl lithium to (76). On
 addition of a ketone, proton-transfer occurred and (118) was formed
 instead of the expected Wittig product. In our case, we form the
 anion of 5-acetylpyrrolidin-2-one(86) which reacts with (76) via
 Michael addition to give the following anion:



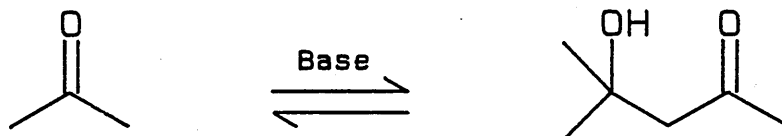
Rather than abstract an α -proton, this system, since the carbonyl
 group is incorporated in the same molecule, is all set for a Wittig
 reaction.

NMR and mass spectral details on pure (87d) were encouraging but micro-analysis was attempted several times and was unsuccessful. It was noticed, however, that the compound appeared to decompose on standing (TLC evidence). In order to analyse (87d) we decided to form the sulphoxide (108) which was a stable solid.

With the preparation of (87d) in hand an attempt was made at desulphurisation of the bicycle using deactivated Raney nickel:



Standard Raney nickel was deactivated by refluxing in acetone for 2 hours⁷⁹ prior to the addition of (87d). Addition of (87d) in an acetone/water solution was then carried out and the mixture refluxed overnight. The catalyst was separated by filtration and TLC of the filtrate showed that two products had been formed. The product which had a R_f value similar to that of the starting sulphide (87d) was assumed to be compound (34). The other product was slightly less polar than (34) and was not visible by U.V. The two products were separated by short column chromatography and analysed by nmr spectrometry. It was seen that the less polar product was the aldol condensation product of acetone, namely 4-hydroxy-4-methyl-2-pentanone or "diacetone alcohol".

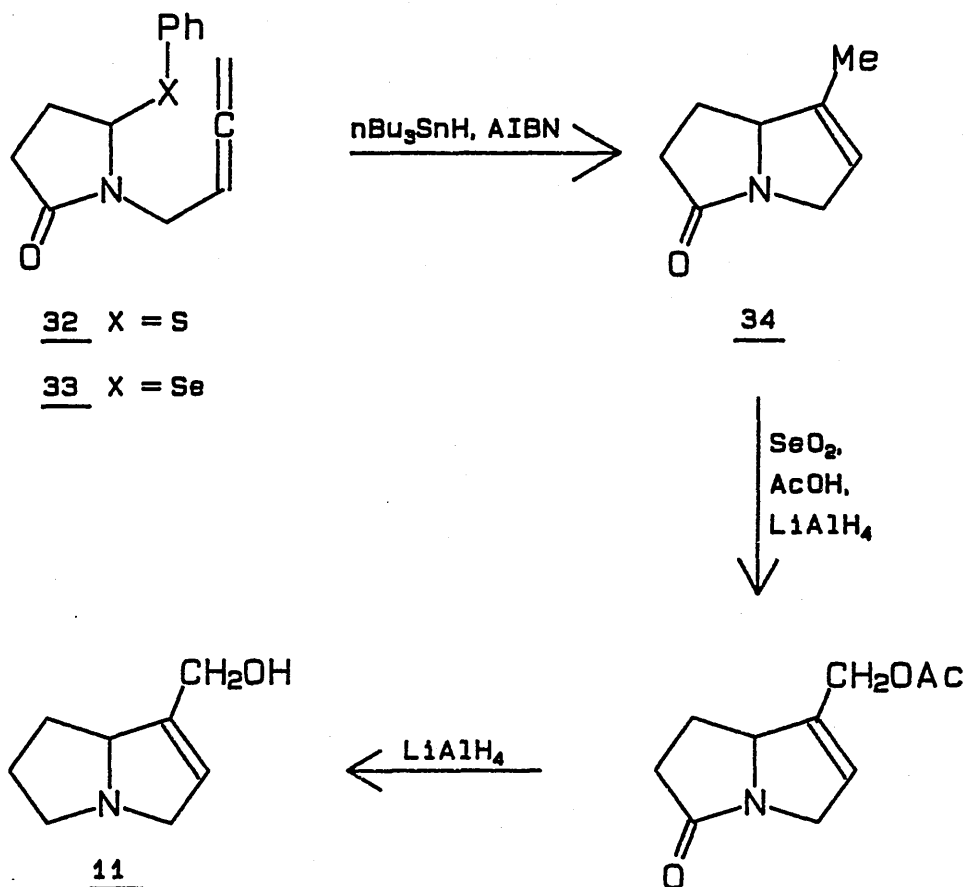


This aldol product was formed in low yields which was not surprising since the overall reaction is an equilibrium process, and the equilibrium constant in most ketone aldol condensations is unfavourable.

from the Raney nickel.

The more polar product was proved to be compound (34). The proton nmr spectrum was in agreement with our initial preparation of (34) using vinylphosphonium salt (71a) (although in the first preparation (34) was present along with triphenylphosphine oxide). The spectrum was also in agreement with that of Hart¹⁷.

Hart used compound (34) in a synthesis of (±) - supinidine (11) (see Chapter 1, Section 1.1.5C).



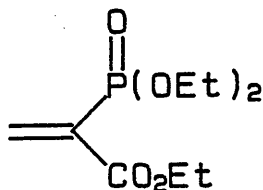
In his synthesis the major cyclisation product (34) was converted to the allylic acetate with selenium dioxide, acetic acid and acetic anhydride. Reduction of the allylic acetate with lithium aluminium hydride gave (±) - supinidine (11).

Since Hart¹⁷ converted (34) into (±) - supinidine, our method constitutes a formal total synthesis of the necine base.

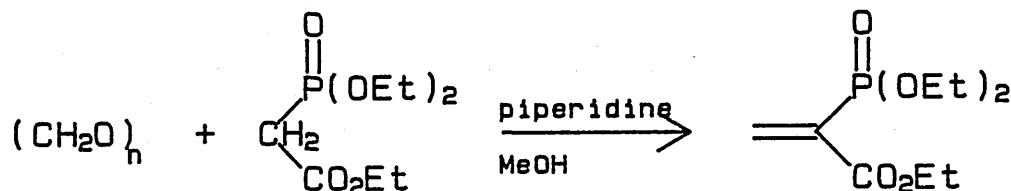
<u>Method</u>	<u>Yield</u>
Acylamino Radical (Hart)	52%
Vinylphosphonium salt (<u>34</u> present with Ph_3PO)	32%
Vinylphosphine oxide followed by desulphurisation	47%
	(From <u>87d</u>)

Although it can be seen that the method of Hart¹⁷ gave the greatest yield of (34), we feel that with further modification the yield of the desulphurisation step could be improved.

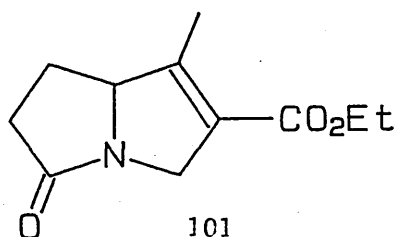
The success of the PO activated olefin synthesis of azabicycle (87) using vinylphosphine oxide (76) prompted us to investigate the reaction of 5-acetylpyrrolidin-2-one (86) with the following vinylphosphonate ester:



Ethyl 2-(diethylphosphono) acrylate was prepared according to the method of Semmelhack et al⁸³.

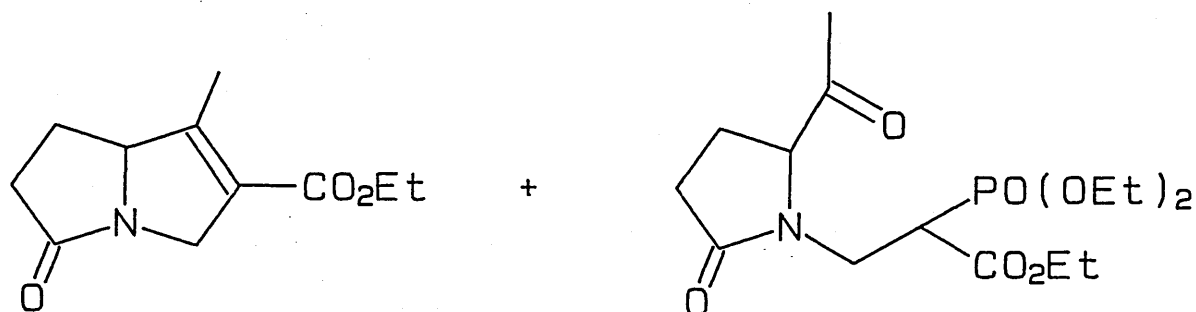


It was thought that reaction of the vinylphosphonate ester with 5-acetylpyrrolidin-2-one (86) would lead to the following bicycle:



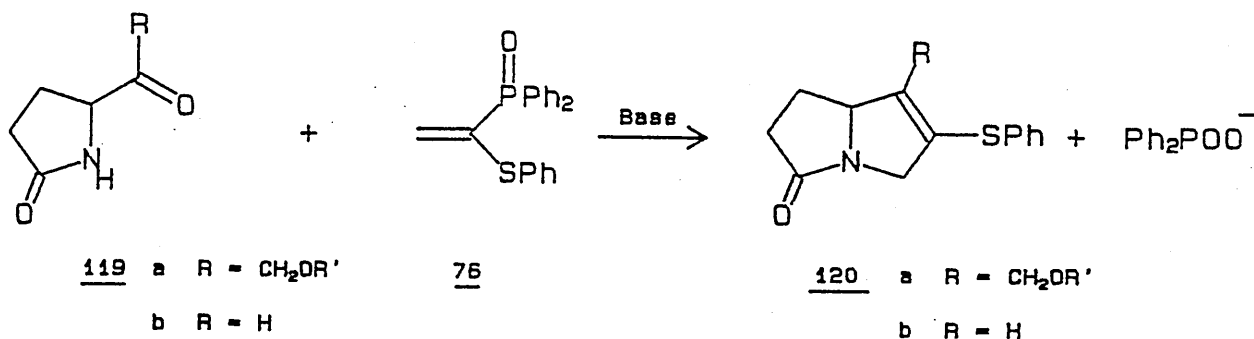
5-acetylpyrrolidin-2-one (86), however, was unsuccessful.

Prolonged refluxing in THF and purification by short column chromatography followed by analysis of the major product by nmr spectrometry indicated that a mixture of the product and the Michael adduct had been formed:

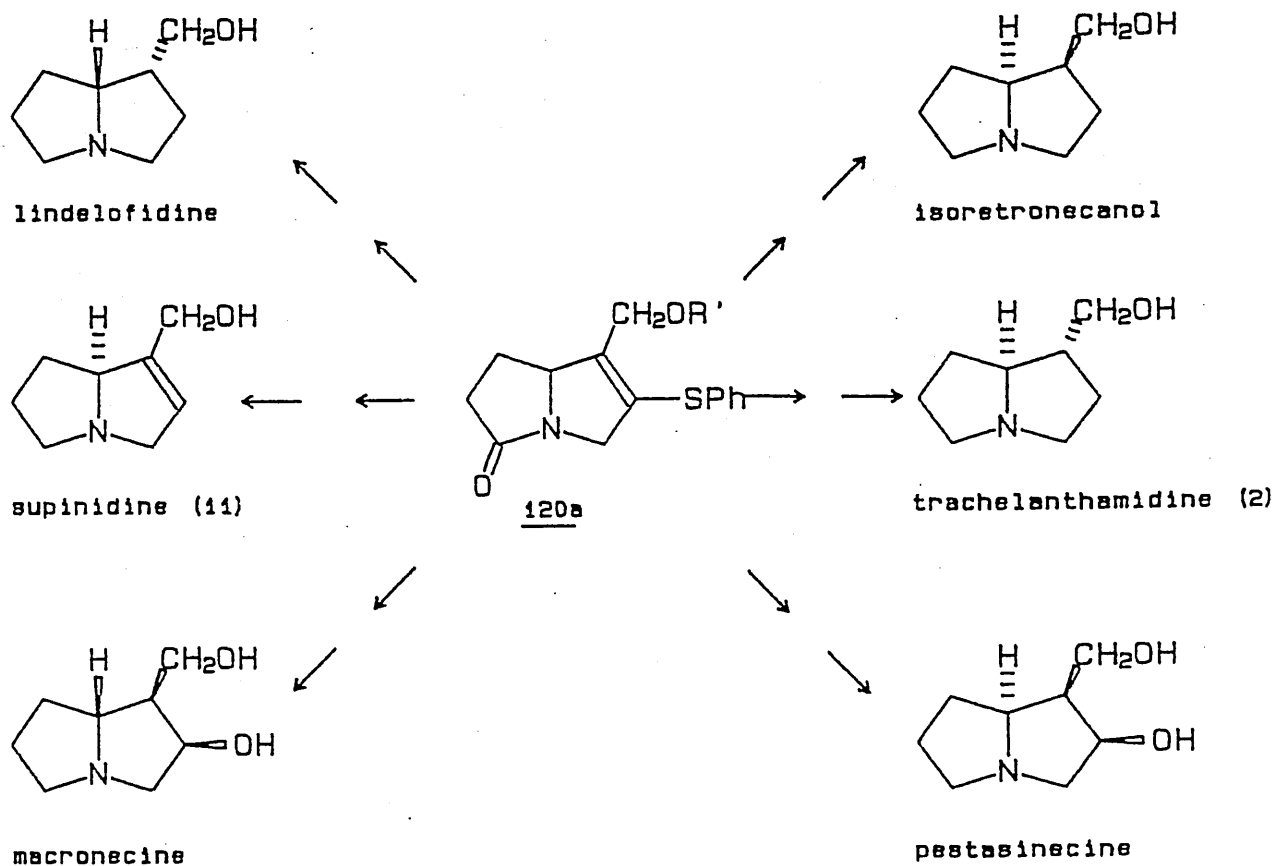


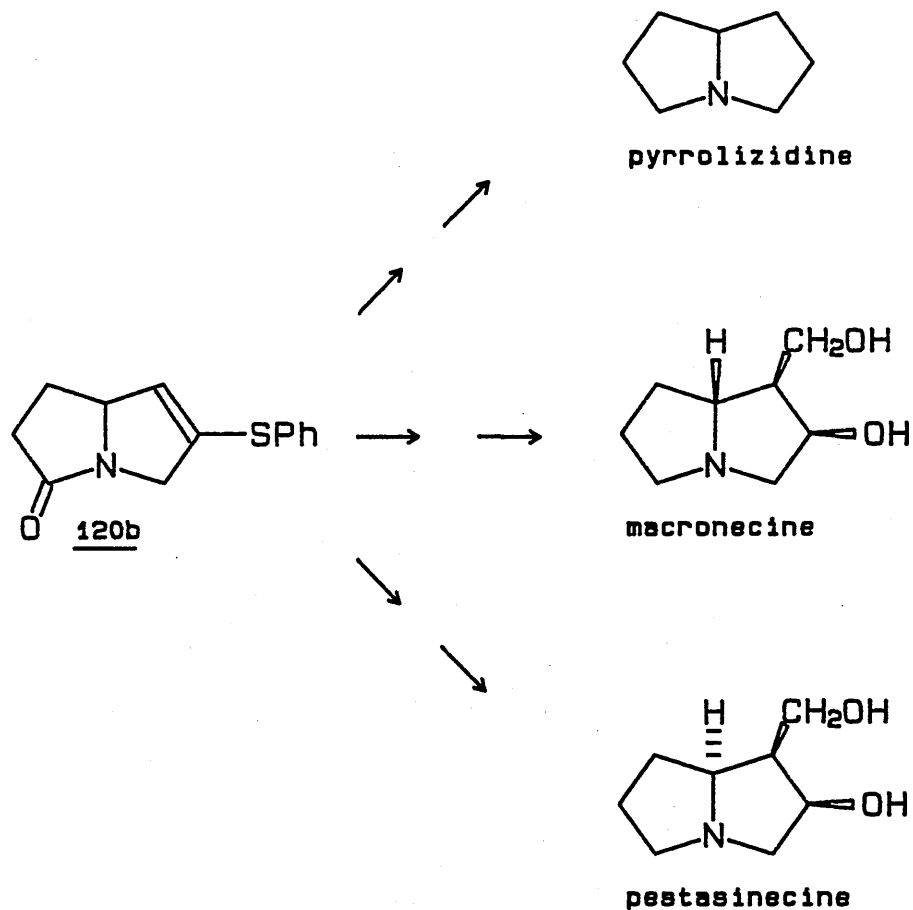
It therefore appears that in our case the most successful PO activated olefin synthesis was that using vinylphosphine oxide (76).

The success of the formation of novel azabicyclic (87d) using vinylphosphine oxide (76) prompted us to look for analogues of 5-acetylpyrrolidin-2-one (86). It was felt that these analogues (119) might be of use in the formation of a variety of necine bases via the Wittig reaction:

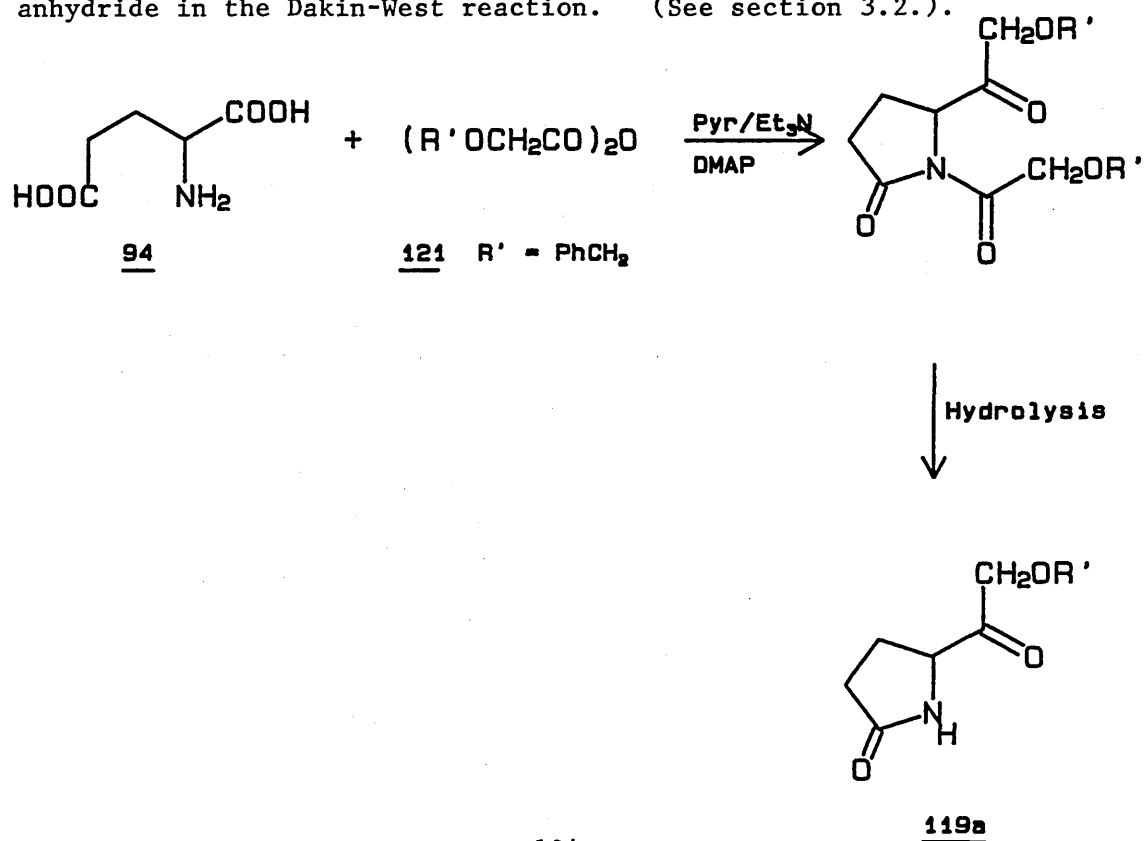


For example, if R=CH₂OR' it was anticipated that azabicyclic (120a) (R=CH₂OR') would be a useful intermediate in the synthesis of a number of necine bases:

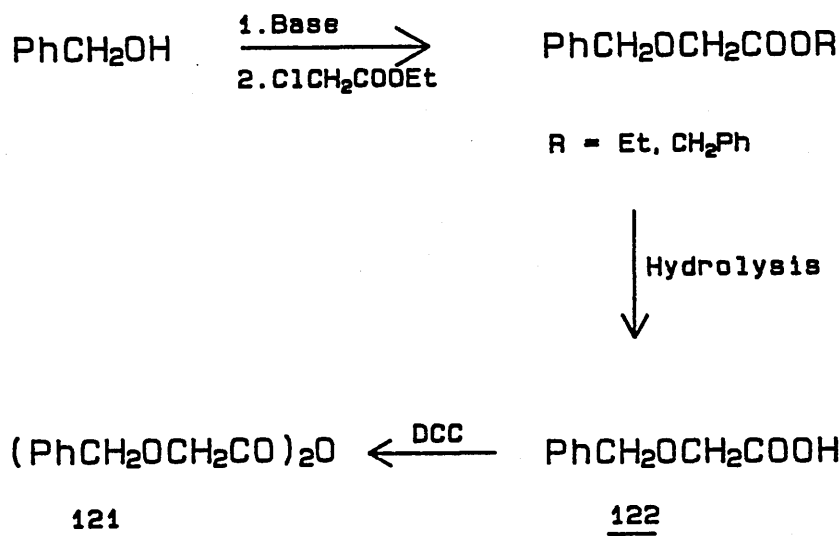




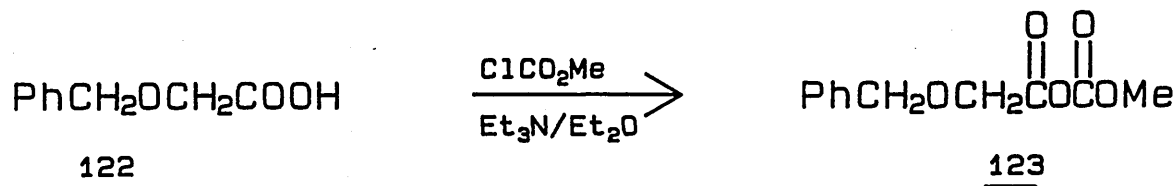
We anticipated that pyrrolidone (**119a**) ($R=CH_2OR'$) might be available by substituting acetic anhydride with another suitable anhydride in the Dakin-West reaction. (See section 3.2.).



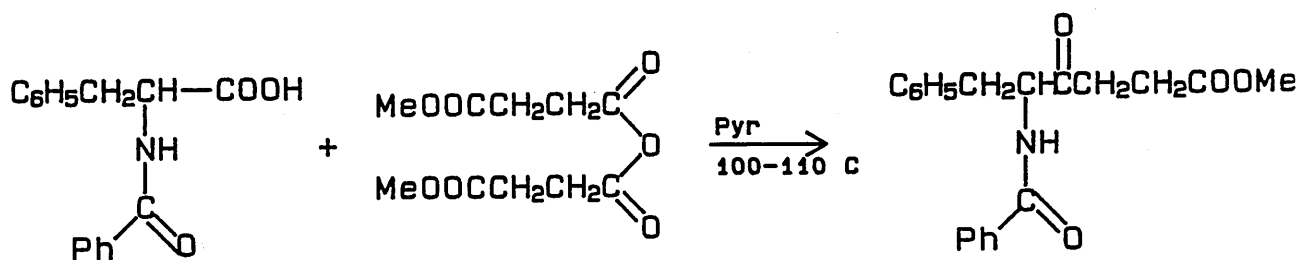
anhydride indicated that benzyloxyacetic anhydride (121) might be a suitable replacement. Monitoring of reactions would be simple since the reagent (121) itself and subsequent products would be U.V. active. Another advantage is the fact that the benzyloxy group is easily removed, and so, for example, azabicyclo (120a) could be converted easily to its hydroxy methyl analogue. Our envisaged synthetic route towards (121) was as follows:



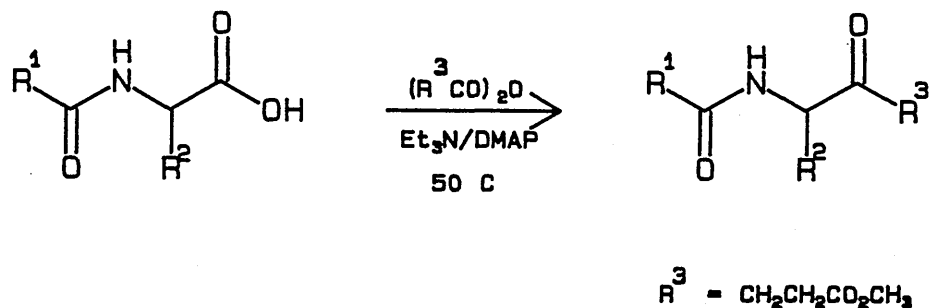
The preparation of benzyloxyacetic acid (122) was carried out by an adaptation of a known procedure⁸⁴. Treatment of the anion of benzyl alcohol with ethylchloroacetate gave, on work-up, a mixture of the ethyl and benzyl esters of benzyloxyacetic acid. The mixed esters were saponified with methanol and aqueous potassium hydroxide to give benzyloxyacetic acid (122). Several attempts were made to form the anhydride (121) using dicyclohexylcarbodiimide (DCC) but were unsuccessful so we turned our attentions to the preparation of a mixed anhydride (123).



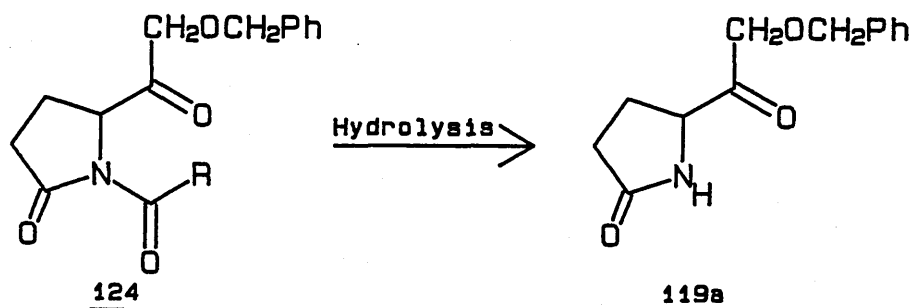
solution of benzyloxyacetic acid (122) and triethylamine in ether. Filtration of the triethylamine hydrochloride and evaporation of the ether in vacuo gave a confusing proton nmr spectrum which seemed to suggest that a mixture of the mixed anhydride (123) and the ordinary anhydride (121) was present. It was found, however, that if the filtrate was evaporated down under reduced pressure at a high temperature then only the mixed anhydride (123) was formed (92% yield). A Dakin-West reaction was attempted between this mixed anhydride (123) and glutamic acid (94) using the same procedure as that used in the preparation of 5-acetylpyrrolidin-2-one (86). When the reaction mixture was distilled, only the mixed anhydride (123) was recovered. This reaction was attempted several times varying the conditions used. It was disappointing to find that in each case only the starting anhydride was recovered but Dakin and West⁶⁶ had stated that the homologues of acetic anhydride were much less reactive than the latter substances. We were encouraged, however, by some recent papers in the literature. In 1985, Cleland and Bennett⁸⁵ used a Dakin-West reaction involving N-benzoyl-phenylalanine, 3,3'-dimethoxycarbonyl propanoic anhydride and pyridine to synthesise methyl-5-benzoylamino-4-oxo-phenylhexanoate.



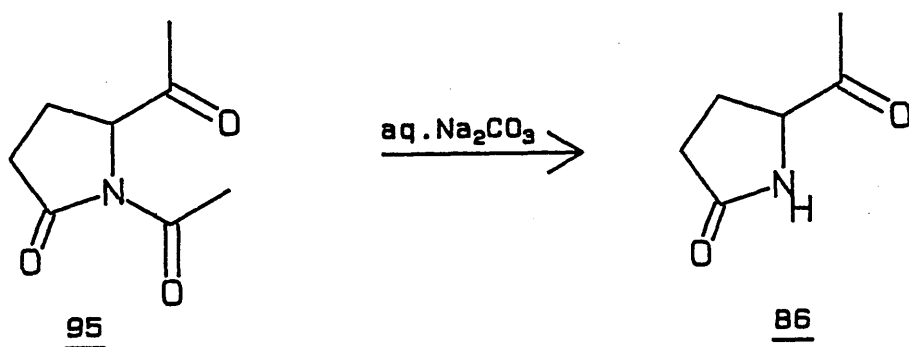
ketomethylene peptide analogues by a modification of the Dakin-West reaction developed by Steglich and co-workers⁷⁶.



As can be seen both procedures employ suitably protected N-acylamino acids and it is known that N-acylated amino acids and subsequently azlactones are intermediates in the Dakin-West reaction (see Section 3.2.). It was therefore envisaged that N-protection of glutamic acid (94) followed by a Dakin-West reaction with the mixed anhydride (123) would give the N-acylpyrrolidone (124). Hydrolysis of (124) with aqueous sodium carbonate should then give pyrrolidone (119).

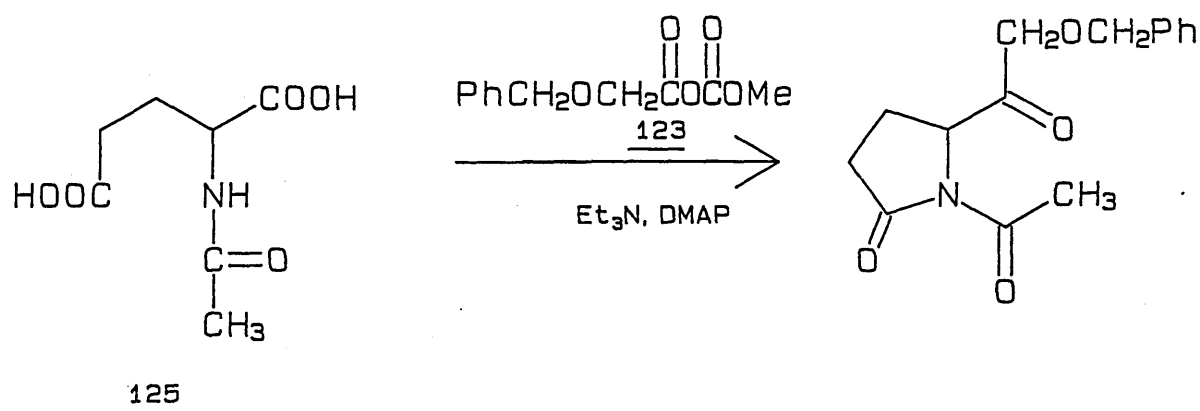


In the choice of a N-protecting group for glutamic acid we decided upon the acetyl group, the reason for this being that Thomas⁶⁵ hydrolysed 1,5-diacetylpyrrolidin-2-one (95) to give 5-acetylpyrrolidin-2-one (86)



and we were hoping to similarly hydrolyse (124).

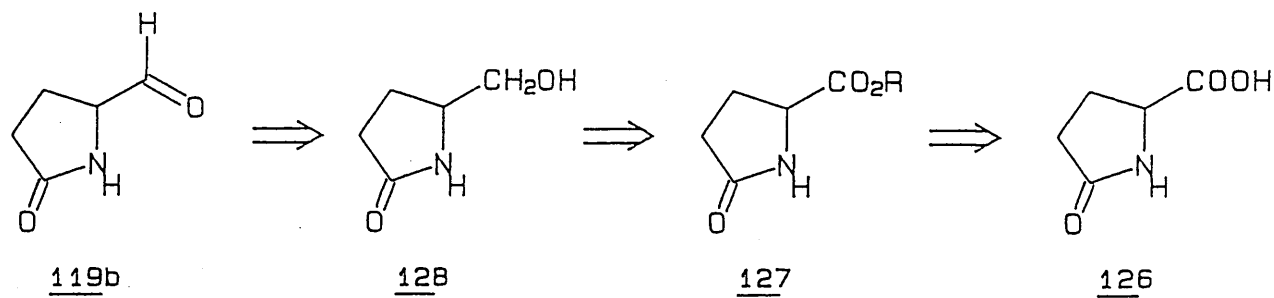
The reaction between the mixed anhydride (123) and commercially available N-acetylglutamic acid (125) was carried out according to McMurray and Dyckes⁸⁶.



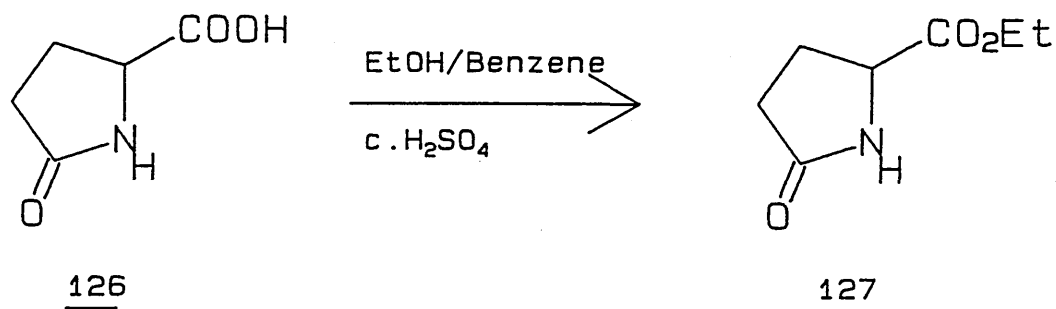
The reaction mixture was stirred at 60 - 70°C for 3 days but the expected evolution of gas was not observed. After purification by column chromatography the mixed anhydride was recovered (> 80% recovery). We therefore decided to try the method of Cleland and Bennett⁸⁵ which used slightly more forcing conditions. The mixed anhydride and pyridine and N-acetylglutamic acid were heated at 110 to 120°C for 24 hours, again no evolution of gas was observed and again the mixed anhydride was recovered on work-up.

It was decided to bring this area of work to a halt due to lack of time.

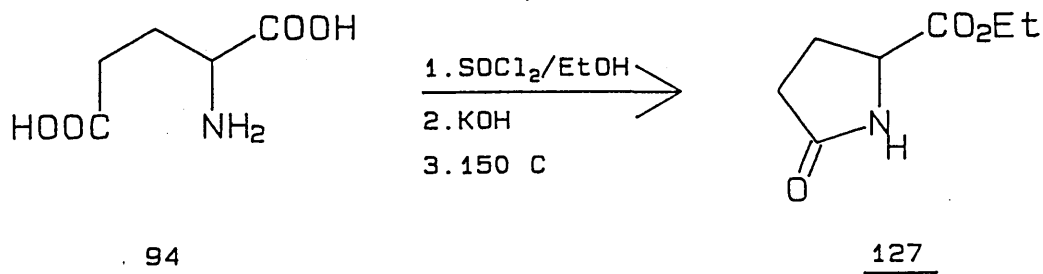
optically pure form since retrosynthetic analysis gave pyroglutamic acid (126) (which is available optically pure) as the precursor.



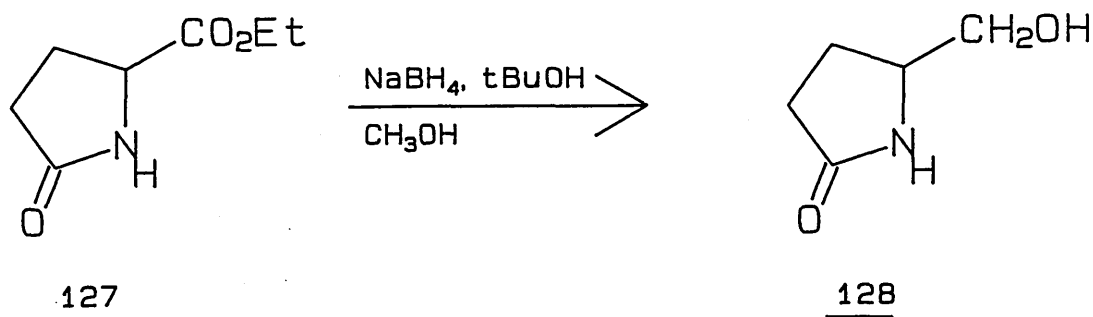
Preparation of 5-carboethoxypyrrolidin-2-one (127) was carried out according to a known procedure⁸⁷.



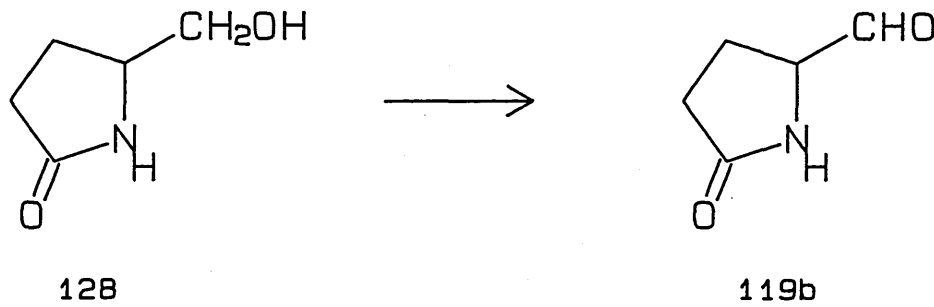
The low yields we obtained (30%) prompted us to look for a more fruitful method. A procedure⁸⁸ was found where both stereoisomers of 5-carboethoxypyrrolidin-2-one were obtainable from glutamic acid by reaction with thionyl chloride in absolute ethanol. If L-glutamic acid was used then the (S)-isomer was formed. Similarly the (R)-isomer could be obtained from D-glutamic acid.



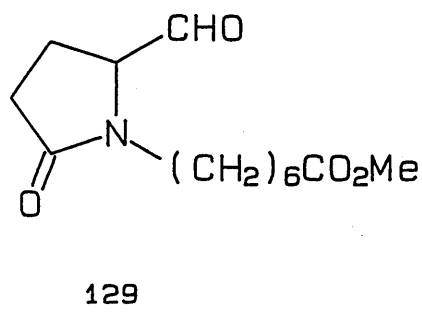
was obtained. Lithium borohydride reduction of ester (127) was attempted but was not a clean reaction (TLC). However, reduction of (127) with sodium borohydride in tertiary butanol and methanol gave (128) (77%)⁸⁹.



All that remained to be accomplished was oxidation of alcohol (128) to aldehyde (119b)

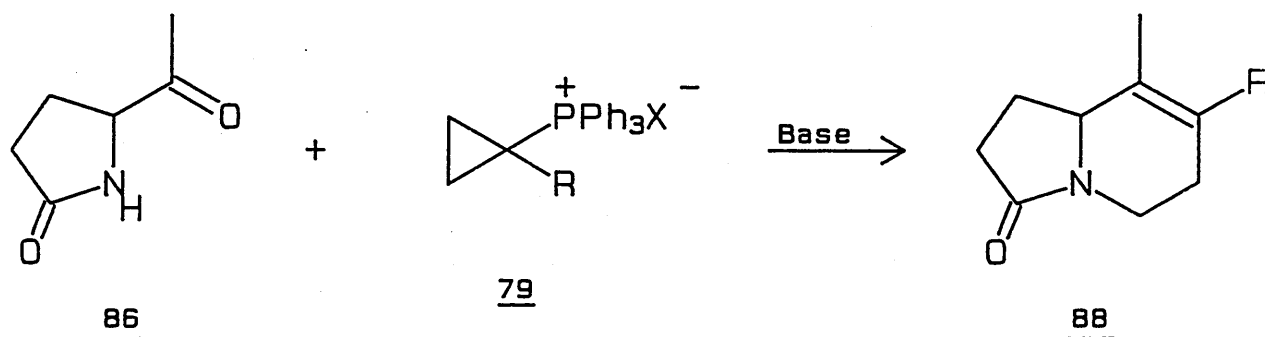


Pyridinium chlorochromate (PCC) oxidation was unsuccessful and so was the Swern procedure. In both cases the work-up seemed to affect the product (TLC). It was assumed that the aldehyde was extremely unstable since similar compounds for example (129) are known to be unstable⁹⁰



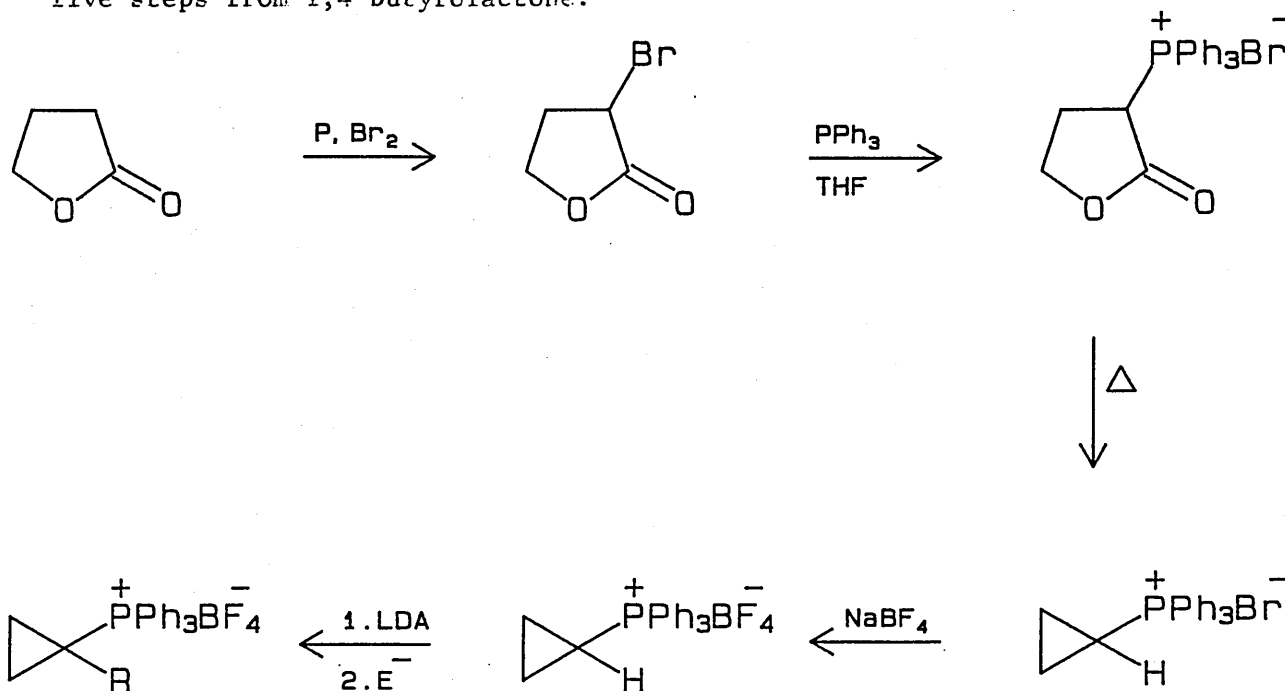
and so this route was abandoned.

As seen in Chapter 2, Section 2.3. page 60, three carbon atoms can be introduced into a molecule via the Wittig reaction by using cyclopropylphosphonium salts (79). It was thought that the 5/6 fused bicycle (88) would be available by reaction of 5-acetylpyrrolidin-2-one (86) with a cyclopropylphosphonium salt (79).



- a R = H , X = Br
 b R = CO₂Et , X = BF₄
 c R = SMe , X = BF₄
 d R = SPh , X = BF₄

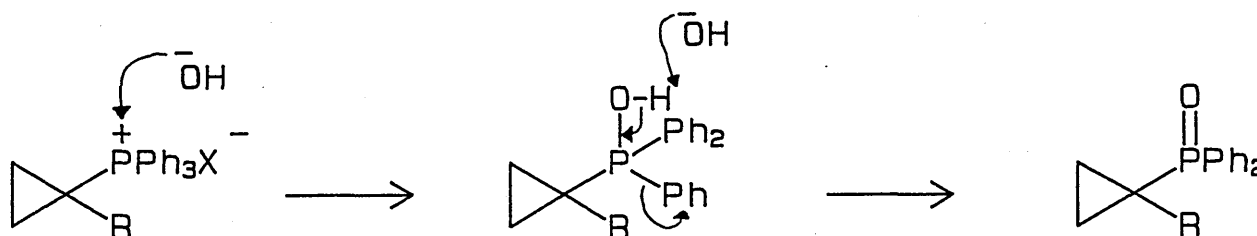
The synthesis of cyclopropylphosphonium salt (79) was carried out in five steps from 1,4-butyrolactone:



E⁻ = electrophile

carried out using phosphorus and bromine⁹². After formation of the phosphonium salt⁹², pyrolysis according to the method of Bestmann⁹³ (by placing sample in an Abderhalden pistol and heating it in vacuo at 199°C for 48 hours)⁵⁶ gave cyclopropylphosphonium bromide (79a). Because of the hygroscopic nature of (79a) it was preferable to work with the fluoroborate salt^{59b}. The cyclopropyl ylide was formed at -30°C and treatment of this ylide with ethyl chloroformate produced (79b). Similarly sulphenylation of the ylide with methyldisulphide or phenylthiosuccinimide gave (79c) and (79d) respectively^{59b}.

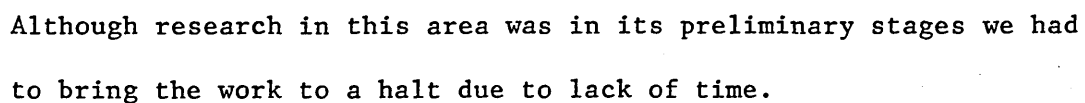
Treatment of the anion of 5-acetylpyrrolidin-2-one (86) with cyclopropylphosphonium salts (79b) or (79c) was unsuccessful. Work-up of the reaction mixture and analysis by proton nmr and mass spectrometry showed that in each case instead of an intramolecular Wittig reaction taking place, hydrolysis of the cyclopropylphosphonium salt occurred to give a cyclopropylphosphine oxide:



We assumed that this problem could be solved by the formation of an α -substituted cyclopropylphosphine oxide, since we had already shown that in our case PO-activated synthesis of 5/5 systems were more successful than those using the corresponding phosphonium salts. (See section 3.4.).

C1CC1P(=O)(O)Br $\xrightarrow{\text{aq. NaOH}}$ C1CC1P(=O)(O)O $\xrightarrow[2. \text{Electrophile}]{1. \text{Base}}$ C1CC1P(=O)(O)R

79a 130



Our studies show that 5/5 nitrogen-bridgehead bicycles were readily available via a PO- activated intramolecular Wittig reaction. We found that the major problem with the use of phosphine oxides, however, was the fact that most of the starting materials and products had similar R_f values and so contamination of products was almost unavoidable. It may be necessary to return to the idea of forming a water-soluble vinylphosphonium salt in order to alleviate this problem.

We feel that the use of 5-acetylpyrrolidin-2-one (86) as a precursor in alkaloid synthesis via intramolecular Wittig reactions is limited due to the presence of the methyl group in the 1-position of the resulting bicycle. Although our initial investigations into the formation of analogues of 5-acetylpyrrolidin-2-one were not successful (mainly due to lack of time) we feel that further study in this area is needed in order to gain access to a wider variety of necine bases.

All our work on the use of 5-acetylpyrrolidin-2-one (86) led to racemic products since (86) itself was racemic. The area of work involving pyroglutamic acid, although unsuccessful, would have given rise to a stereoselective synthesis. Again we feel that investigations involving stereoselectivity would be beneficial.

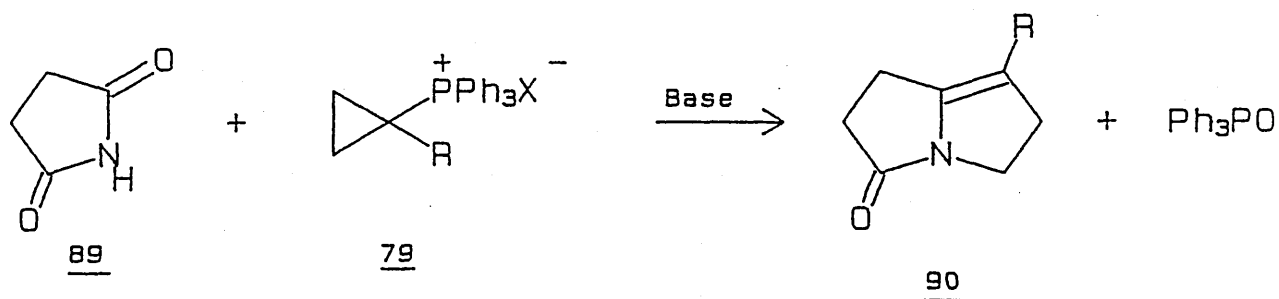
The difficulties seen in the formation of 5/6 fused systems with both cyclopropylphosphonium salts and cyclopropylphosphine oxides and lack of time suggest that this area would also benefit from further study.

CHAPTER 4

The use of succinimide in the synthesis of heterocyclic systems

- 4.1. Introduction
- 4.2. Attempted synthesis of novel 5/5 fused bicycles from succinimide via an intramolecular Wittig reaction
- 4.3. Attempted synthesis of novel 5/6 fused bicycles from succinimide via an intramolecular Wittig reaction
- 4.4. Summary and future work

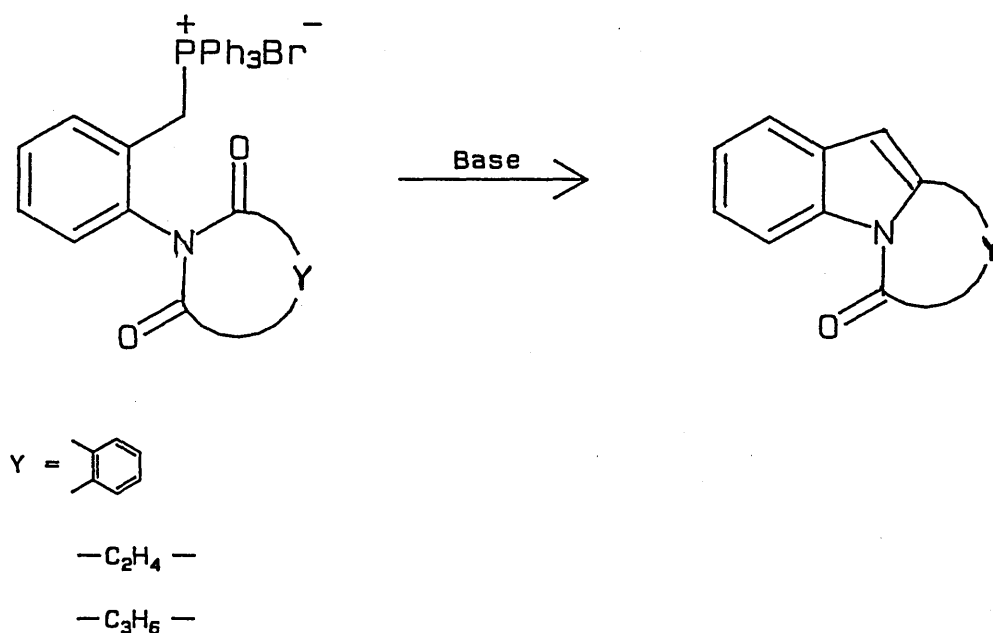
It has already been stated, (Chapter 2, section 2.5.), that imides are known to undergo the Wittig reaction⁶⁴ and so we hoped to make use of this fact in our work on azabicyclic formation. We anticipated that the 5/5 fused bicyclic (90) would be available from succinimide (89) and cyclopropylphosphonium salt (79) via an intramolecular Wittig reaction:



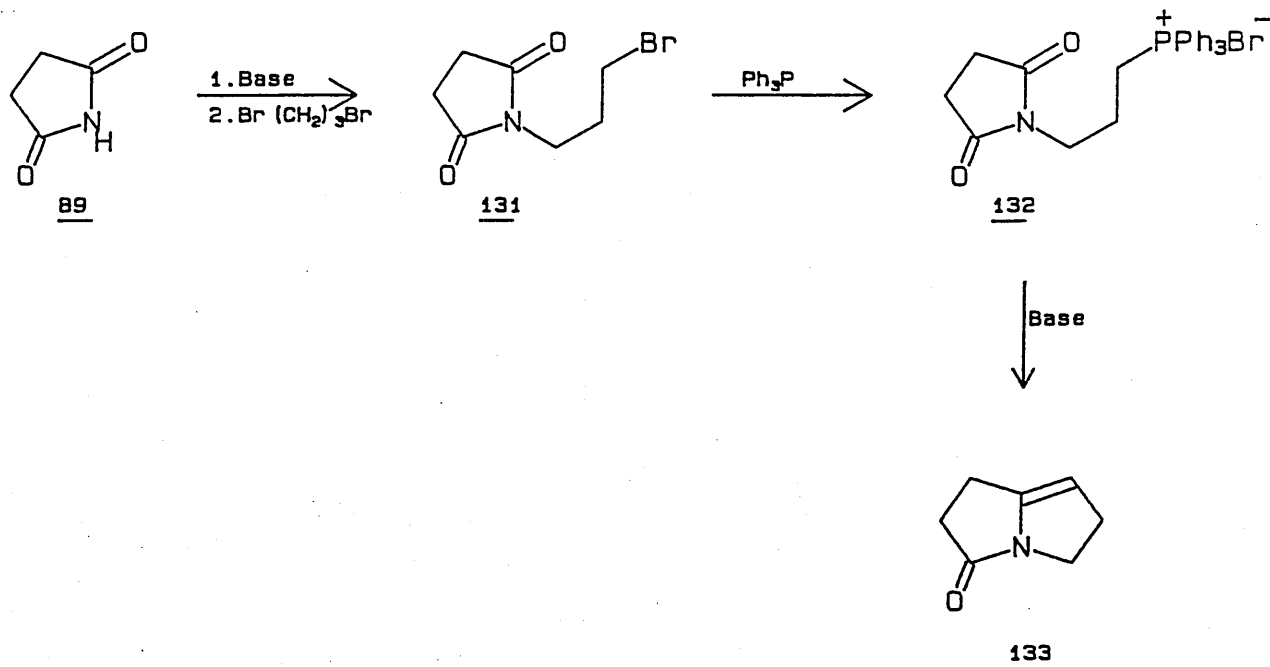
- a R = H , X = Br
- b R = CO₂Et , X = BF₄
- c R = SMe , X = BF₄
- d R = SPh , X = BF₄

The above pentannulation reaction was attempted several times using either THF or DMF as solvent. In each instance, several products were formed (TLC evidence), none of which appeared to be predominant (density TLC). Separation of the products using short column chromatography and analysis by proton nmr showed that (90) had not been formed. We were confused as to why the reaction had failed and assumed that either ring opening of the cyclopropylphosphonium salt (79) by the anion of succinimide was not realised, or ring opening had occurred but the intramolecular Wittig had not. We decided to investigate these possibilities in the hope that a solution to these problems would lead to success in the Wittig reaction.

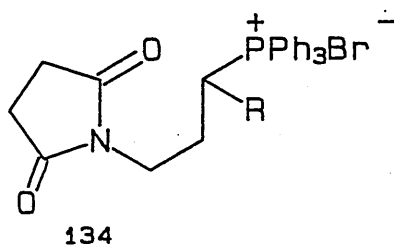
In order to investigate the failure of our Wittig reaction, we decided to use a modification of Crenshaw and Zimmer's route to indoles⁹⁴. In their communication they reported a simple synthesis of the pyrrolo [1,2-a] - indole ring system and the 6,7,8,9- tetrahydropyrido [1,2-a]- indole analogue via an intramolecular Wittig reaction between an imide and phosphorus ylide:



succinimide (89) according to the following scheme:

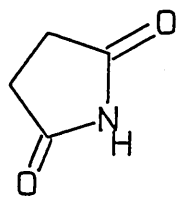


Phosphonium salt (132) was formed in good yields from (131). On treatment with base, however, several products were observed and again not one appeared to be the expected Wittig product (133). Since phosphonium salt (132) has no substituents α to the phosphorus, the ylide formed on treatment with base would not be stabilised. This was thought to be the reason why the reaction did not appear to work. A decision was made to attempt a synthesis of an α - substituted phosphonium salt (134).



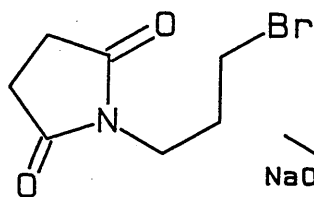
- a R = SPh X = Cl
b R = CO₂Me X = Br

It was envisaged that (134a) would be available via two different routes:



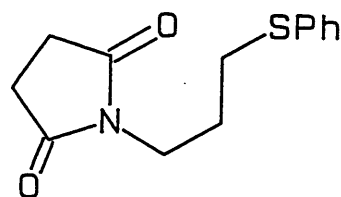
89

1. NaH
2. Br(CH₂)₃Br



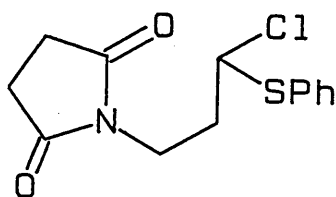
131

NaOMe,
MeOH,
PhSH

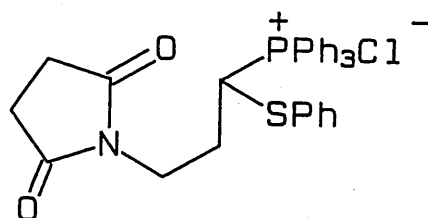


136

α-chlorination



PPh₃



134a

HOCH₂CH₂CH₂Br

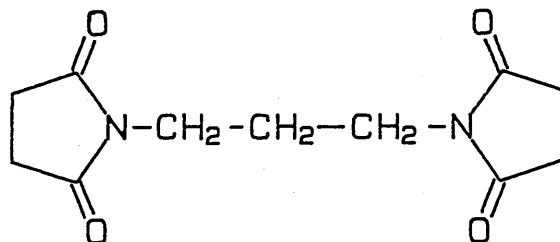
NaOMe,
MeOH,
PhSH

HOCH₂CH₂CH₂SPh

135

89,
Ph₃P, DEAD
'Mitsunobu'

the anion of succinimide followed by sulphenylation of the resulting bromide (131). Although phenyl sulphide (136) was available by this route we found that the first step, that is the alkylation of succinimide, was low yielding. On work-up it was seen that the low yield was due to the formation of the following "dimer".

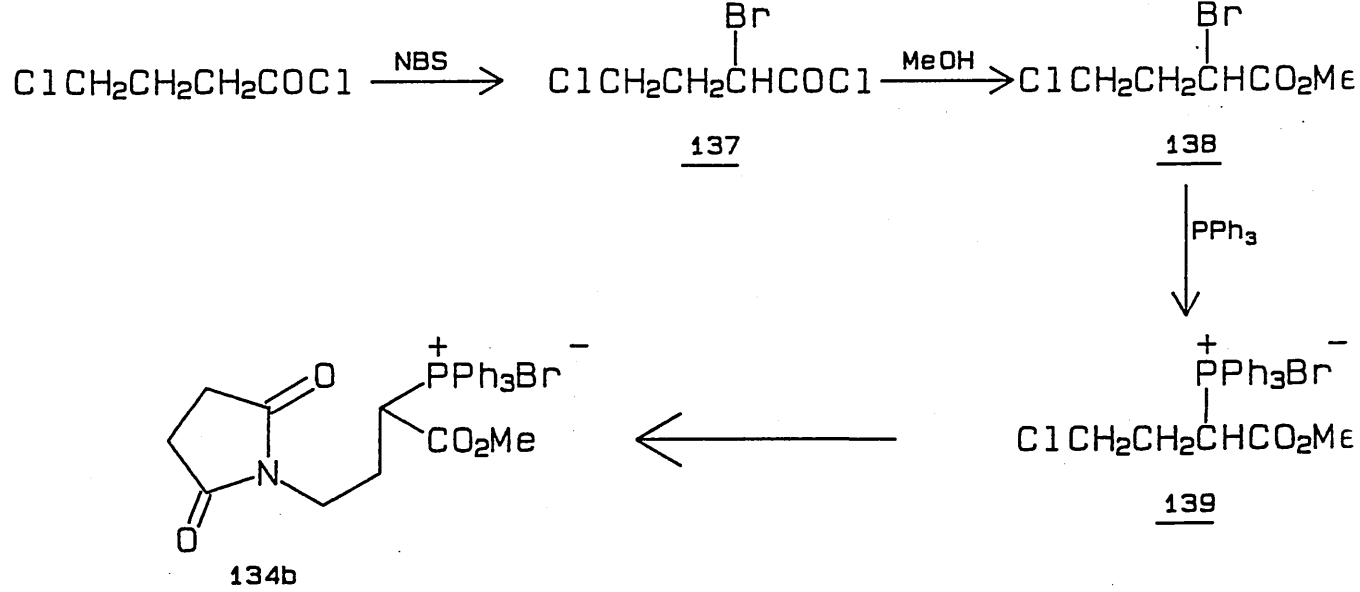


We found that Route B provided greater yields of the phenyl sulphide (136). After conversion of 3-bromopropan-1-ol to phenyl sulphide (135), Mitsunobu coupling⁹⁵, that is the one stage formation of alkyl succinimides from alcohols, gave (136) in good yields.

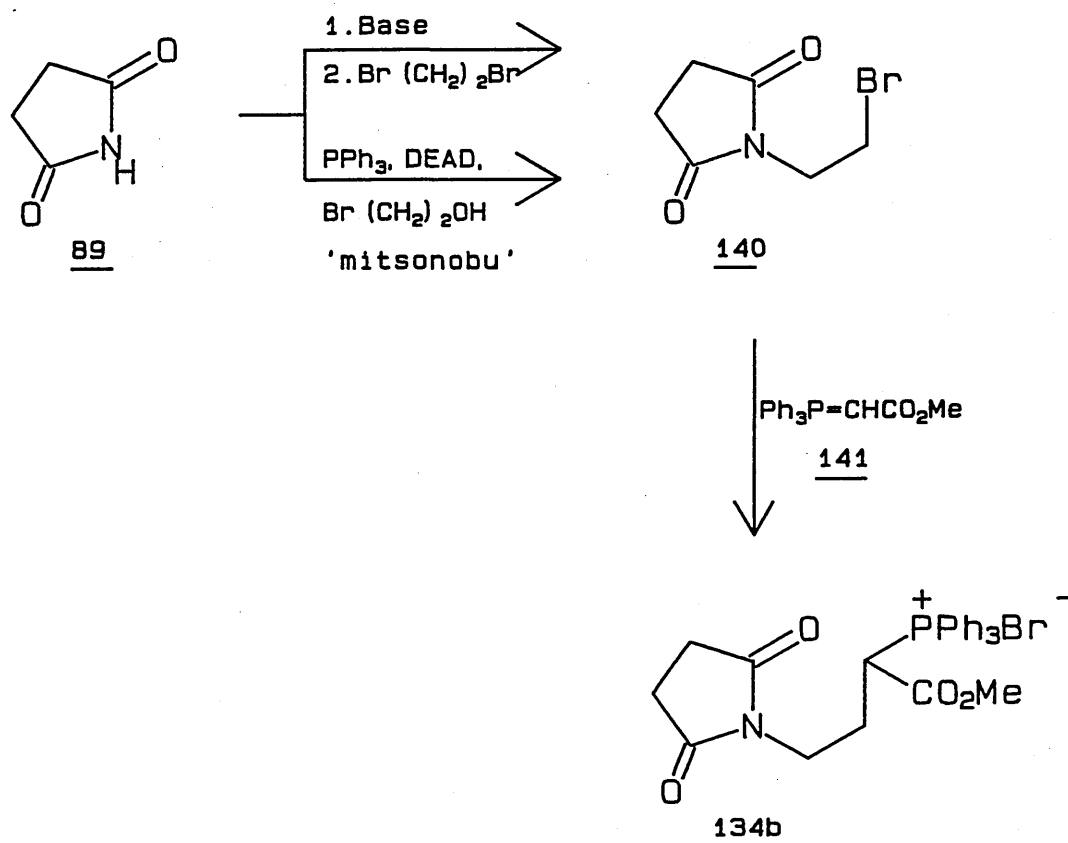
With the preparation of (136) in hand all that remained to be accomplished was the α -chlorination of (136) followed by formation of phosphonium salt (134a).

chloride in various solvents. On each occasion TLC indicated that several products had been formed and since α -chloroalkylphenyl sulphides are very reactive it was inadvisable to separate the mixture by short column chromatography. Since phosphonium salts are usually crystalline it was thought that maybe the phosphonium salt could be formed in situ, that is, after α -chlorination immediate reaction with triphenylphosphine should produce the phosphonium salt (134a). Again we found isolation of the product impossible. The presence of the succinimide ring was considered to be the problem affecting the chlorination process and so it was decided that α -chlorination of phenyl sulphide (135) should be attempted. Again this was unsuccessful and so we decided to protect the hydroxyl group in (135) before chlorination. Several protecting groups were tried, including tetrahydropyranyl, acetyl, and α -ethoxyethyl, but we were still disappointed to find that it was difficult to α -chlorinate.

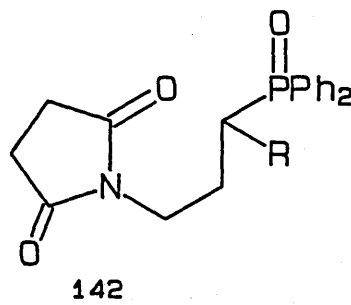
It is possible, however, to α -halogenate acid halides. Harpp and Gleason⁹⁶ have reported an efficient method for the α -bromination of acid chlorides using N-bromosuccinimide (NBS) and also α -chlorination and α -iodination of acid chlorides using N-chlorosuccinimide (NCS) and molecular iodine with a trace of HI, respectively. We assumed that it might be possible to synthesise (134b) utilising this method:



α -bromination of 4-chlorobutryl chloride with NBS took place readily, yielding >80% of the α -bromo acid chloride (137). Reaction of (137) with methanol⁹⁷ gave 61% of the α -bromo methyl ester (138). Formation of the phosphonium salt 139 however proved difficult, even upon trituration with sodium-dried ether a crystalline material could not be formed. It was therefore thought that (134b) might be available via a different route:



...the separation of the product (140) from the diethylazodicarboxylate by-product proved extremely difficult. Thus the anion of succinimide (89) was formed and reaction with 1,2-dibromoethane gave 43% of (140). The addition of methoxycarbonylmethylenetriphenylphosphorane (141) to (140) was attempted several times without success. In each case the starting materials were recovered. We came to the conclusion that since phosphonium salt (134b) was proving difficult to isolate we needed to turn our attention to the possibility of forming the phosphine oxide analogue of (134), namely (142).



a R = SMe

b R = SPh

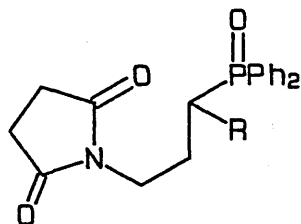
It has already been stated that phosphine oxides are usually crystalline compounds which are generally more reactive in the Wittig reaction than the corresponding phosphonium salts (see Chapter 2, section 2.1. and Chapter 3, section 3.4.). Our envisaged synthetic route to phosphine oxide (142) is outlined below:



143

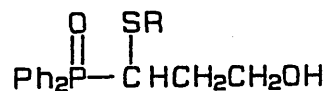
144

1. nBuLi
2. RSSR
TMEDA



142

89. PPh₃, DEAD

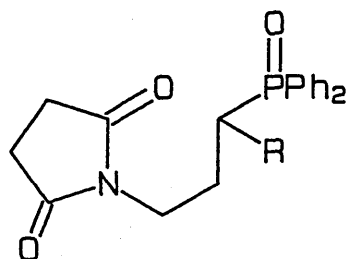


145

a R = SMe

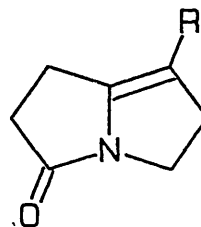
b R = SPh

Our method, adapted from Grayson and Warren⁸², showed that primary alkylidiphenylphosphine oxide (144) was readily available from triphenylphosphine via alkylation and hydrolysis. The anion of (144), formed with n-butyllithium in the presence of tetramethylethylenediamine (TMEDA), reacted readily with dimethyl or diphenyl sulphide to give the sulphenylated phosphine oxides (145) in good yields. Mitsunobu⁹⁵ coupling of the sulphenylated phosphine oxides (145) with succinimide to give (142) was also high yielding. It was extremely disappointing to find that on treatment with base, (142) failed to undergo a Wittig reaction to give azabicyclic (90).



142

Base

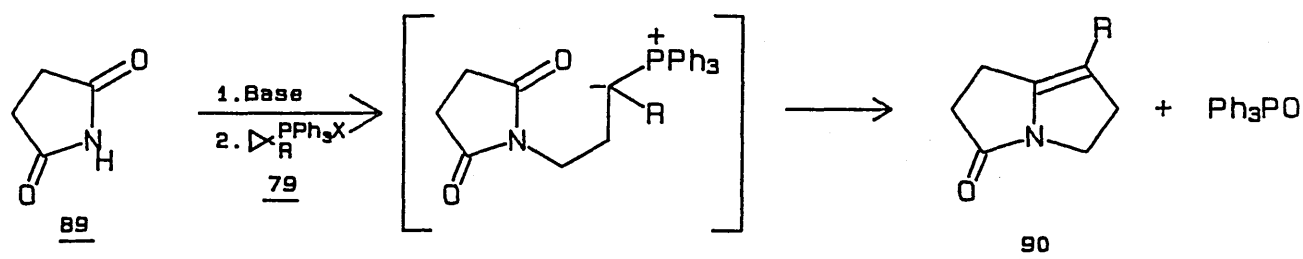


90

a R = SMe

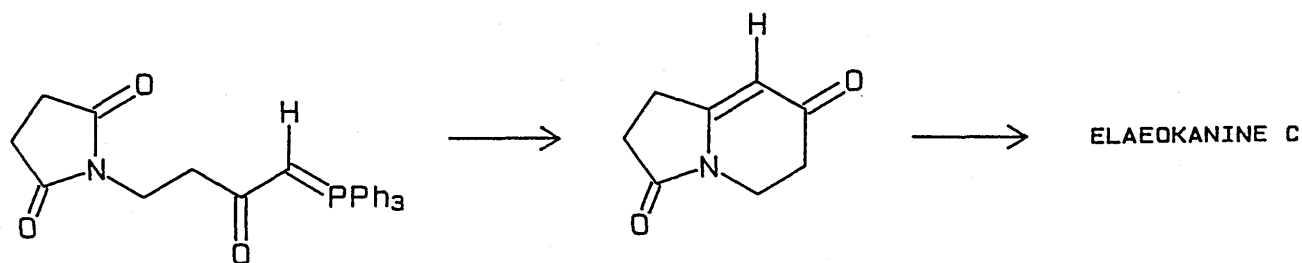
b R = SPh

a solution to the problem we encountered with our initial reaction:

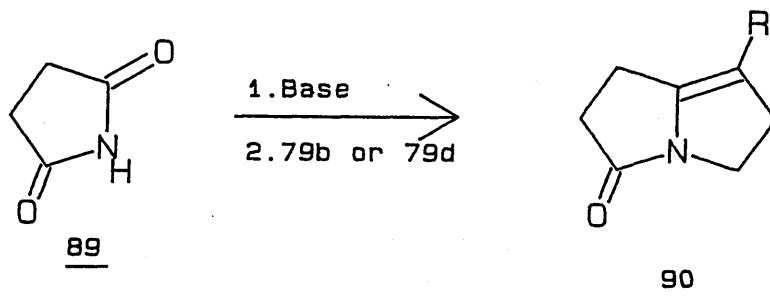


When a comparison was made between the proton nmr spectrum of the above attempted cyclisation reaction and the actual proton nmr of phosphine oxide (**142**), there appeared to be definite similarities. We were able to assume that ring opening of the cyclopropylphosphonium salt (**79**) by the anion of succinimide had occurred, but for some reason the Wittig reaction on the imide carbonyl had not.

While our work was in progress a paper appeared describing Elaeocarpus alkaloid synthesis using cyclizing imide olefinations⁹⁸:



paper to another intramolecular Wittig reaction performed by Flitsch⁹⁹ on imide carbonyl groups (which we had unfortunately not located in our preliminary literature search), discussing the reaction between cyclopropylphosphonium salts (79b) and (79d) with succinimide (89).



b R = CO₂Et 84%

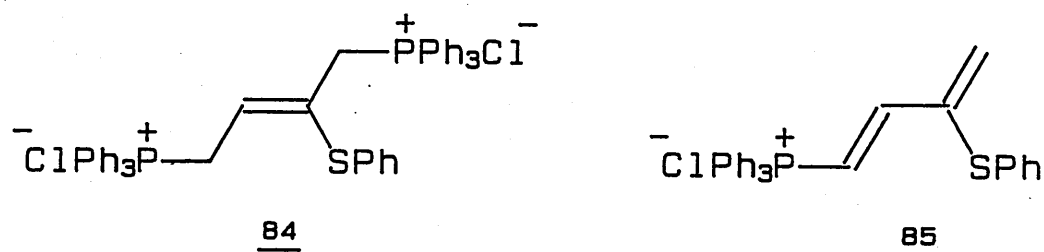
d R = SPh 45%

Flitsch again used refluxing xylene to perform the reaction.

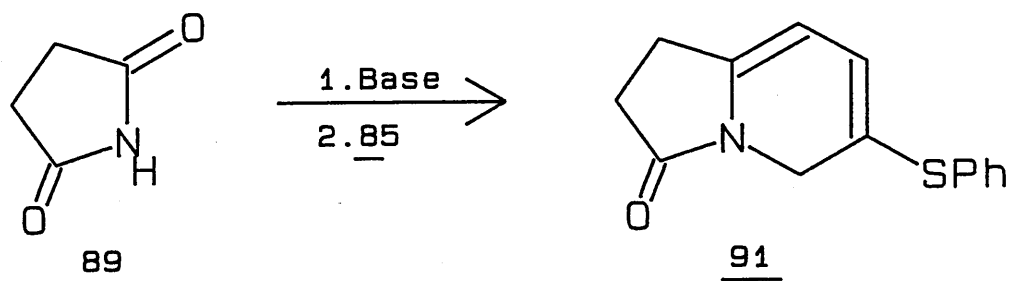
It therefore appears that for intramolecular Wittig reactions on imide carbonyl groups to be successful harsh conditions are needed. We were not surprised that our work in this area was unsuccessful since we had been using refluxing THF/approximately 6 hour reaction time. Due to the fact that this paper had already been published we decided there was no point continuing our work in this area.

As discussed in Chapter 2, Section 2.4., incorporation of four carbon atoms into a cycloalkene can be accomplished by the use of butadienylphosphonium salts.

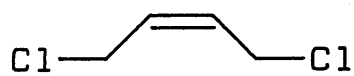
We had hoped to form a highly functionalised azabicyclic using the bis phosphonium salt (84)⁶³ as a precursor to the dienylphosphonium salt (85).



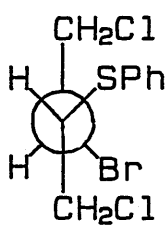
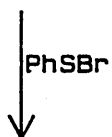
We anticipated that the 5/6 fused bicycle (91) would be available from succinimide (89) and the transient dienylphosphonium intermediate 85 via an intramolecular Wittig reaction.



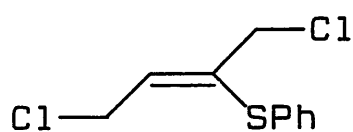
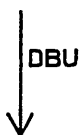
The preparation of (84)¹⁸ was carried out according to the method of Pariza and Fuchs⁶³.



146

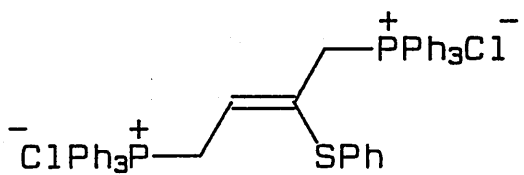


147

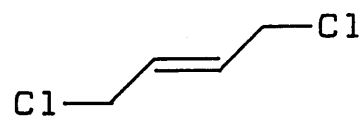


148

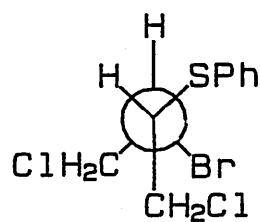
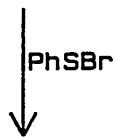
PPh₃



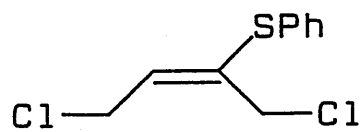
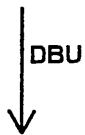
84



149

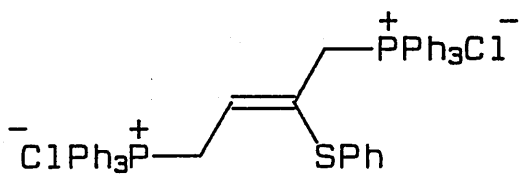


150



151

PPh₃



bromide gave threo-trihalo sulphide (147) in essentially quantitative yield as a colourless oil. Similarly the isomeric dichloride (149) reacted with phenylsulphenylbromide to produce erythro trihalosulphide (150). Treatment of (147) with D.B.U. (1,8-diazabicyclo [5.4.0.] undec-7-ene) at -50°C in ether, followed by allowing the solution to gradually warm to room temperature gave the E-dichlorovinylsulphide (148). The D.B.U. elimination of HBr from (150) was less efficient than from (147). Treatment of either (148) or (51) with 2.2 equivalents of triphenylphosphine in D.M.F. at 25°C for 3 days gave the same bis phosphonium salt (84).

The annulation reaction between succinimide (89) and the transient butadienylphosphonium salt (85) was attempted several times in either THF or DMF without success. In each case several products were formed (TLC evidence) and separation of the products by short column chromatography proved difficult. Analysis of the separate fractions showed that the expected product (91) had not been formed.

Although this area of work was not extensively studied we feel that similar conclusions can be drawn as for the reaction between succinimide (89) and cyclopropylphosphonium salts (79), that is that the temperature employed was not high enough to effect cyclisation.

In contrast to Flitsch's^{98,99} work, our studies on the intramolecular Wittig reaction of succinimide and cyclopropylphosphonium salts (79) were unsuccessful. After more detailed investigations were made, however, we came to the following conclusion:

It appears that for an intramolecular Wittig reaction to occur on an imide carbonyl group, quite forcing conditions are necessary. All our work was carried out under fairly mild conditions. However, under these mild conditions ring-opening of the cyclopropylphosphonium salt did occur. The limiting factor in our case appeared to be the actual attack of the resulting ylide on the imide carbonyl group due to the mild conditions employed. Although we feel that there is no need for work to be continued in this area, it did give us valuable insight into intramolecular Wittig reactions on imide carbonyl groups.

Our work on the formation of 5/6 systems utilising the transient butadienylphosphonium salt (85) was not extensively studied. We feel that research in this area should be continued bearing in mind the conclusions we arrived at above, that is, the employment of forcing conditions to effect the Wittig reaction.

Infrared spectra were obtained on a Pye-Unicam SP3-100 spectrophotometer. Samples were prepared as potassium bromide (KBr) discs or liquid films. ^1H NMR spectra were recorded on Bruker WP80 SY and Jeol PMX 60 SI spectrometers. Samples were prepared in the solvent stated in each method. Microanalyses were determined at the City University London. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Low resolution mass spectra were recorded on a VG Micromass 30F spectrometer.

IR data is given in cm^{-1} . NMR data is given on the δ scale using tetramethylsilane as the internal reference. Abbreviations used for the form of the signal are as follows:- s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

Rapid column chromatography and column chromatography were performed on Merck 7734 and Merck 7736 silica gel respectively. Thin-layer chromatography was performed on Merck 5554 Alufolien Kieselgel 60F₂₅₄ plates. Solvents for column chromatography were distilled before use. Petrol refers to that fraction of petroleum spirit boiling between 40 and 60°C.

Dry THF was obtained by distillation from potassium metal. Dry diethyl ether was obtained by distillation from LiAlH_4 . Dry CH_2Cl_2 was distilled from calcium hydride and stored over 4A molecular sieves. Dry diisopropylamine was distilled from calcium hydride and stored under nitrogen over 4A molecular sieves. Dry DMF was obtained by heating over calcium hydride followed by distillation under reduced pressure onto 4A molecular sieves.

n-Butyl lithium was standardised before use and its molarity is given where needed. Sodium hydride was obtained as a 60% dispersion in mineral oil. Dry methanol was distilled from sodium.

All reactions requiring inert atmospheres were done under nitrogen.

Hyflo super cell filter aid was obtained from BDH chemicals.

Vinyltriphenylphosphonium bromide (71a)

Vinyltriphenylphosphonium bromide was commercially available from Aldrich.

1-Methylthiovinyltriphenylphosphonium chloride (71c)^{45,46}

A solution of triphenylphosphine (262g, 1 mol) and methylthiomethyl chloride (96.6g, 1 mol) in acetonitrile (11) was refluxed for 5 hours. The solution was allowed to cool to room temperature and the resulting white crystalline solid was filtered off. The filtrate was reduced in volume by half and a second crop of product was obtained on cooling to 0°C. Total yield of methylthiomethyltriphenylphosphonium chloride (293g, 86.7%). mp 218 - 220°C. (lit⁴⁶ 218 - 220°C) IR (KBr) 3060, 2850, and 2750. ¹H NMR (CDCl₃) 2.15 (s, 3H), 5.3 (d, 2H) and 7.8 (m, 15H).

To a solution of this phosphonium salt (50g, 0.14mol) in dry acetonitrile (250 ml) was rapidly added N,N-dimethylmethyleammonium chloride (28.1g, 0.3mol). The mixture was refluxed under nitrogen until nmr analysis indicated complete reaction (ca 60 h). The solvent was removed and the residue was taken up in chloroform (250 ml) and washed with brine (3 x 50 ml). The chloroform layer was dried (MgSO₄) and the solvent was removed to afford a pale yellow oil which crystallised on trituration with ether to give (71c) 43.5g, 84%. The salt was recrystallised from chloroform-ethyl acetate mp 142 - 144°C (lit⁴⁶ 142-144°C) ¹H NMR 2.7 (s, 3H), 6.1 - 7.2 (m, 2H) and 7.8 (m, 15H).

This was prepared as for the methylthio derivative (71c) above, from triphenylphosphine (262g, 1mol) and iodomethylphenylsulphide (250g, 1mol). Phenylthiomethyltriphenylphosphonium iodide was obtained as a yellow solid (466g, 91%). The salt was recrystallised from chloroform-ethyl acetate mp 127 - 128°C (lit⁴⁶, 127 - 128)
'H NMR (CDCl₃) 5.38 (d, 2H), 7.4 (m, 5H) and 7.85 (m³, 15H).
The reaction of this phosphonium salt with N, N -dimethylmethylen ammonium chloride was complete in ca 15 h. The product (71d) was obtained as a yellow solid (89%) and was recrystallised from acetonitrile - ethyl acetate mp 145 - 146°C (lit⁴⁶ 145 - 146°C) 'H NMR (CDCl₃) 6.35 - 7.0 (m, 2H), 7.55 (m, 5H) and 7.95 (m, 15H).

1,5 - Diacetylpyrrolidin-2-one (95)

To L-glutamic acid (7.3g, 0.05 mol) in acetic anhydride (25ml) was added 4-dimethylaminopyridine (50mg, 0.4m mol) and triethylamine (25ml). The reaction mixture was stirred at 60°C for 8 hours and distilled under reduced pressure. On standing a white solid formed which was recrystallised from ether. 6.59g, 78%. mp 60-62°C (lit⁷⁶ 58-62°C). IR (KBr) 3410(br), 1735, 1690, 1370, 1290 and 1175. 'H NMR (CDCl₃) 1.66 - 2.83 (m, 4H), 2.2 (s, 3H), 2.4 (s, 3H) and 4.63 - 4.9 (m, 1H).

1,5-diacetylpyrrolidin-2-one (95) (2.22g, 0.013 mol) and sodium carbonate (5.58g, 0.053 mol) were dissolved in water (30ml) and the solution stirred at 20°C for 5 hours. The pH was adjusted to 7 using dilute hydrochloric acid, and the product extracted with dichloromethane (200ml) using a continuous extraction apparatus for 25 hours. After drying (MgSO_4) and concentration under reduced pressure, the organic phase gave an off-white solid. 1.21g, 73%. mp 73-75°C (Lit⁶⁵ 74 - 76°C) IR (KBr) 3190 (br), 1710, 1420, 1380, 1350, 1280, 1245 and 1185. ¹H NMR (CDCl_3) 1.76 - 2.90 (m, 4H), 2.3 (s, 3H), 4.07 - 4.53 (m, 1H) and 7.16 (br.s, 1H).

5,6,7,7a-tetrahydro-1-methyl-2-phenylthio-3H - pyrrolizin-5-one

(87d) from (71d)

Sodium hydride (44 mg, 1.1mmol, 60% dispersion in oil) was placed in a 25ml 3-necked round bottomed flask and washed with petrol. THF (2ml) was added followed by 5-acetylpyrrolidin-2-one (86)⁶⁵ (127mg, 1mmol). The reaction mixture was stirred for 15 mins and then phosphonium salt (71d)^{45,46} (1.048g, 2mol) was added. The reaction mixture was heated under reflux for 5 hours and then partitioned between water and chloroform. The chloroform layers were dried (MgSO_4) and evaporated. Chromatography with ethyl acetate-petrol (50:50) afforded two products. The first to be eluted was a 5/7 fused bicycle (see Chapter 3, Section 3.3.) formed via a Michael-Michael ring closure reaction, 12mg, 3%. IR (KBr) 3410 (br) and 1690. ¹H NMR (CDCl_3) 1.8 (s, 3H), 1.8-3.0 (m, 7H) 3.3 - 3.8 and 4 - 4.7 (m, 3H) and 7.23 (s, 10H) Microanalysis found: C, 68.57; H, 6.33; N, 3.49. $\text{C}_{22}\text{H}_{23}\text{NOS}_2$ requires :C, 69.25; H, 6.08, N, 3.67.

oxide. Total yield of mixture 454mg. Ratio of (87d) to Ph_3PO was 1:1.8 (from ^1H NMR integration and GC/MS peak areas). Yield of (87d) was therefore 142 mg, 58%. IR (KBr) 3405 (br) and 1700. ^1H NMR (CDCl_3) Ph_3PO 7.25 - 7.62 (m, 9H) and 7.70 (m, 6H). (87d) 1.8 (m, 3H), 1.93 - 3.0 (m, 4H), 3.30 - 3.80 (m, 1H,) 4.05 - 4.76 (m, 2H) and 7.15 (s, 5H). GC/MS (87d) m/z 245, 230, 189, 136, 121 and 55 Ph_3PO , m/z 277, 201/199, 185/183, and 77.

For alternative preparation see (87d) from (76).

5,6,7,7a - tetrahydro-1-methyl-2- methylthio-3H-pyrrolizin-5-one
(87c)

This was prepared as for (87d) above, from 5-acetylpyrrolidin-2-one (86)⁶⁵ (127mg, 1mmol), sodium hydride (44mg, 1.1mmol) and phosphonium salt (71c)^{45,46} (740mg, 2mmol). Total yield of mixture 162mg. Ratio of (87c) to Ph_3PO was 1:1.5 (from ^1H NMR integration and GC/MS peak areas). Yield of (87c) was therefore 49.5mg, 27%. IR (KBr) 3410 (br) and 1690 ^1H NMR (CDCl_3) Ph_3PO 7.25 - 7.62 (m, 9H), and 7.70 (m, 6H). (87C) 1.73 (m, 3H) 1.83 - 2.80 (m, 4H), 2.16 (s, 3H), 3.43 - 3.93 (m, 1H) and 4.3 - 4.76 (m, 2H). GC/MS (87c) m/z 183, 168, 136, 127, 124, 112 and 55. Ph_3PO m/z 277, 201/199, 185/183 and 77.

(86)⁶⁵ (127mg, 1mmol), sodium hydride (44mg, 1.1mmol) and phosphonium salt (71a) (738mg, 2mmol). Total yield of mixture 151mg. Ratio of (34) to Ph_3PO was 1:1.7 (from ^1H NMR integration). Yield of (34) was therefore 34 mg, 25%. IR (KBr) 3400 (br) and 1700. ^1H NMR (CDCl_3) Ph_3PO 7.06 - 7.5 (m, 9H) and 7.66 (m, 6H). (34) 1.7 (m, 3H), 1.9 - 2.9 (m, 4H), 3.2 - 3.8 (m, 1H), 4.0 - 4.6 (m, 2H) and 5.26 (br.s, 1H).

For alternative preparations see (34) from desulphurisation of (87d) and reference 17.

Reduction of 5,6,7,7a - tetrahydro-1-methyl-2-phenylthio-3H-pyrrolizin -5-one (87d)

Lithium aluminium hydride (340mg, 8.95 mmol) in dry THF (25ml) was heated under reflux with stirring for approximately 15 mins until most of the LiAlH_4 had dissolved. A solution of the mixture of (87d) and Ph_3PO (1.736g ie 0.571g of 87d, 2.33 mmol) in THF (15ml) was added slowly at such a rate that the solvent refluxed gently without external heating. When the addition was complete, the mixture was stirred and refluxed for 18 hours. The reaction was followed by TLC until all the starting material had reacted. Water was then carefully added to the reaction mixture and the mixture extracted with chloroform. The organic layer was then extracted into dilute hydrochloric acid. The aqueous layer was then basified with dilute sodium hydroxide and the product extracted with chloroform.

a more polar solvent was used ie ethyl acetate -methanol 90:10 to perform column chromatography.

The major product, a brown oil (426mg) gave a complex ^1H NMR spectrum. MS analysis was also complex, it appeared that two components were present with m/z 273 and 256.

5,6,7,7a -tetrahydro-1-methyl-2-phenylsulphinyl-3H-pyrrolizin- 5-one
(108)

(a) from (87d) and Ph_3PO

A solution of the mixture of (87d) and Ph_3PO (3.73g ie 1.226g of 87d, 5mmol) in dichloromethane/THF (25ml) was cooled to -78°C and *m*-chloroperbenzoic acid (1.079g, 5mmol, 80%) was added. The solution was stirred at -78°C and gradually allowed to warm to room temperature. The mixture was stirred at room temperature for 6 hours and then water (25ml) was added. The organic layer was separated, washed with sodium bicarbonate, dried (MgSO_4) and then evaporated. Chromatography with ethyl acetate - petrol (50:50) gave the sulfoxide (108) IR (KBr). 3450br, 3110, 3050, 2980, 2920, 2850, 1700, and 1050. ^1H NMR (CDCl_3) 2.08 (m,3H), 1.5 - 2.73 (m,4H) , 3.5 - 4.8 (m,3H) and 7.3 (s,5H). MS m/z 261, 244, 135 and 55.

The diastereoisomer of 108 was also formed but was present along with Ph_3PO . The formation of the diastereoisomer was proved by oxidation of a pure sample of (87d) (see below).

Procedure as above using pure (87d) (453mg, 1.85 mmol) and m-chloroperbenzoic acid (400mg, 1.85 mmol). Chromatography gave (108) 385mg, 79% IR (KBr). 3480br, 3105, 3060, 2990, 2910, 1700 and 1060. ¹H NMR (CDCl₃) 2.08 (m, 3H), 1.5-2.73 (m, 4H), 3.5-4.8 (m, 3H) and 7.3 (s, 5H). MS m/z 261, 244, 135, 55. Microanalysis found : C, 68.67; H, 6.74; N, 5.11. (Best of several attempts). C₁₄H₁₅NO₂S requires : C, 64.34; H, 5.78; N, 5.35.

4-bromobenzylbromide (110)

4-bromotoluene (51.3g, 0.3mol) was dissolved in carbon tetrachloride (150ml). N-bromosuccinimide (54g, 0.3mol) was added and the resulting mixture refluxed for 90 hours. (A few crystals of benzoyl peroxide were added to initiate the reaction). The reaction mixture was filtered and the solvent removed under reduced pressure. On cooling a solid formed which was recrystallised from ethanol, 42.64g, 57%, mp 61-62°C (lit 63°C - Aldrich).

The reaction was followed by ¹H nmr which showed a decrease in the singlet at 2.35 and an increase in the singlet at 4.5.

4-bromobenzyl-diisopropylamine (111)

4-bromobenzylbromide (110) (25g, 0.1mol) was dissolved in diisopropylamine (125g) and was treated with methyl iodide (1ml) as a catalyst. The resulting mixture was refluxed for 4 days.

hydrochloric acid, neutralised with sodium hydroxide, and re-extracted with ether. The ether layer was dried (MgSO_4) and the solvent removed under reduced pressure. Distillation gave 23.8g, 90% of pure (111) as a yellow oil. bp $95-105^\circ\text{C}$ at 0.3 mm Hg (lit⁷⁸ 65°C at 0.1mm Hg). IR (liquid film) 3000, 2960, 1480, 1380, and 1200. ^1H NMR (CDCl_3) 1.0 (d,12H), 3.0 (septet,2H), 3.6 (s,2H) and 7.3 (m,4H).

4-diisopropylaminomethyltriphenylphosphine (109)

4-bromobenzyl diisopropylamine (111)⁷⁸ (11g, 0.04mol) was added dropwise to a suspension of lithium (0.65g, 0.09mol) in 60ml of an 80% ether/20% THF solution under nitrogen, at such a rate as to maintain a steady reflux. To initiate the reaction a few crystals of iodine were added and the reaction warmed gently. After complete addition, the mixture was refluxed for 2 hours. Chlorodiphenylphosphine (10.1g, 0.046 mol) was added at such a rate as to maintain reflux, and then stirred for 1 hour after addition. The reaction mixture was shaken with 2 x 150ml 5% aq hydrochloric acid, and the aqueous layer basified with sodium hydroxide and re-extracted with 3 x 150ml ether. The ether layers were dried (MgSO_4) and the solvent removed. A dark brown oil, 14.2g, was obtained. IR (liquid film) 3080, 2960, 1600, 1580, 1430, 1380, 1360. Purification by distillation did not yield the required product, but ^1H NMR of one of the fractions indicated that benzyl diisopropylamine had been formed - ^1H NMR 1.0 (d,12H) 3.0 (septet, 2H), 3.6 (s,2H) and 7.3 (m,5H).

A solution of chlorodiphenylphosphine (50.75g, 41.29ml, 0.23mol) in dry ether (125ml) was added dropwise to a stirred solution of absolute ethanol (23g, 0.5mol) and anhydrous pyridine (27g, 0.345mol) at 0°C. The mixture was left overnight at room temperature and filtered. The filter cake was thoroughly washed with ether (ca 250ml) and most of the solvent was removed at reduced pressure. Distillation gave ethoxydiphenylphosphine (112) bp 108-116°C at 0.5mmHg (lit⁸⁰ 161.2°C at 10mmHg), 42.08g, 79% IR (liquid film) 3040, 2950, 2900, 2850 and 2220 NMR (CDCl₃) 1.23 (t, 3H), 3.76 (q, 2H) and 7.0 - 7.5 (m 10H).

Chloromethylphenylsulphide (113)

A solution of thioanisole (83.9g, 80ml, 0.675mol) in dichloromethane (500ml) was heated to reflux. A solution of sulphuryl chloride (90.0g, 54ml, 0.667mol) in dichloromethane (150ml) was added dropwise over 1.25 hours. Reflux was continued for 2 hours and then the reaction allowed to cool to room temperature. The solvent was removed under reduced pressure to give (113), 104g, 98.6% as a yellow liquid bp 64-66°C at 0.2mm Hg (lit⁸¹ 66°C at 0.2mm Hg) IR (CCl₄) 720, 690 and 653. ¹H NMR (CCl₄) 4.82 (s2H) and 7.3 (m, 5H).

Ethoxydiphenylphosphine (112) (42.00g, 0.10mol) and chloromethylphenylsulphide (113)⁸¹ (31.38g, 0.198 mol) were heated together under nitrogen at 150°C for 1.5 hours. On cooling, a solid separated which was recrystallised from ethyl acetate-petrol to give phosphine oxide (114) 51.84g, 89%. mp 104-106°C (lit⁸² 106-107°C) ¹H NMR (CDCl₃) 3.73 (d, 2H) and 7.1-7.9 (m, 15H).

Diphenyl-1-(phenythioethyl)phosphine oxide (115)

Diphenyl(phenylthiomethyl)phosphine oxide (114)⁸² (22.69g, 0.07mol) in dry THF (300ml) and TMEDA (9.29g, 12.03ml, 0.08mol) was treated with n-butyllithium (52ml, 1.54M, 0.08mol) at -78°C. The orange anion was quenched after 12 mins with methyl iodide (11.36g, 4.98ml, 0.08mol) and the resulting pale yellow solution was allowed to warm to room temperature over 0.5 hour. Aqueous ammonium chloride (100ml) was added, and the product extracted with chloroform. The organic extracts were washed with dilute hydrochloric acid and dried (MgSO₄). Evaporation gave a pale yellow solid (115) which was recrystallised from ethyl acetate petrol, 20.11g, 85%. mp 153-154°C (lit⁸² 154-155°C). IR (KBr) 1580, 1475, 1445 and 1180. ¹H NMR (CDCl₃) 1.54 (dd, 3H), 3.38 (m, 1H), 7.2 (m, 5H) and 7.4 - 8.0 (m, 10H).

m-chloroperbenzoic acid (1.07g, 5mmol, 80%) in dichloromethane (10ml) was added to a solution of 1-phenylthioethyldiphenylphosphine oxide (115)⁸² (1.69g, 5mmol) in THF (15ml) cooled to -78°C. The reaction mixture was stirred for 1 hour at -78°C and allowed to warm to room temperature, when it was washed with aq sodium bicarbonate and dried (MgSO₄). The solvents were removed at reduced pressure to give a viscous oil. Chromatography with ethyl acetate gave the sulfoxide (116)⁵⁵ as a mixture of diastereoisomers in quantitative yields. ¹H NMR 1.1-1.2 (m, 3H), 3.38-3.84 (m, 1H) and 7.2-8.2 (m, 15H).

1-Phenylthiovinyl-diphenylphosphine oxide (76)

Acetic anhydride (0.56ml, 5.89 mmol) and methanesulphonic acid (10 drops) were added to a solution of 1-phenylsulphinylethyl-diphenylphosphine oxide (116)⁵⁵ (1.77g, 5.0mmol) in dichloromethane (50ml) and the mixture stirred at room temperature for 8 days. The reaction mixture was poured into aq. sodium carbonate, extracted with dichloromethane, dried (MgSO₄), and the crude product chromatographed with ethyl acetate to give vinyl sulphide (76)⁵⁵, 1.26g, 75% ¹H NMR 5.63 (d, 1H), 6.16 (d, 1H) and 7.15-8.25 (m, 15H).

from (76)

Sodium hydride (0.16g, 4mmol, 60% dispersion in oil) was placed in a 50ml 3-necked round bottomed flask and washed with petrol. THF (20ml) was added followed by 5-acetylpyrrolidin-2-one (86)⁶⁵ (0.5086g, 4mmol). The reaction mixture was stirred for 15 minutes and then phosphine oxide (76)⁵⁵ (0.672g, 2mmol) was added. The reaction mixture was heated under reflux for 2 hours and then partitioned between water and chloroform. The chloroform layers were dried (MgSO₄) and evaporated. Chromatography with ethyl acetate-petrol (50:50) afforded the product (87d), 0.35g, 71% as a colourless oil. IR (liquid film) 3010 (br) and 1690 ¹H NMR (CDCl₃) 1.83 (m,3H), 1.90-3.00 (m,4H) 3.30-3.83 (m,1H) 4.0-4.80 (m,2H) and 7.10 (s,5H) MS m/z 245, 230, 189, 136, 121 and 55. Microanalysis found C, 66.31; H, 5.66; N, 5.59 (Best of several attempts) C₁₄H₁₅NOS requires: C,68.53; H,6.16; N,5.18. For alternative preparation see (87d) from (71d).

Standard Raney nickel (20g) was deactivated by refluxing in acetone (50ml) for 2 hours. A solution of bicycle (87d) (0.98g, 4mmol) in acetone/water was added and the mixture refluxed overnight. The catalyst was separated by filtration and TLC of the filtrate showed two products had been formed. Separation of the two products by column chromatography using ethyl acetate - petrol (50:50) gave initially the aldol condensation product of acetone, that is, 4-hydroxy-4-methyl-2-pentanone (0.637g) ¹H NMR (CDCl₃) 1.2 (s,6H), 2.1 (s,3H), 2.63 (s,2H) and 3.63 (br s, 1H). The second product to be eluted as a colourless oil was (34), 258 mg, 47%. ¹H NMR (CDCl₃) 1.70 (m,3H), 2.0-3.0 (m, 4H), 3.20 - 3.90 (m,1H), 4.0-4.6 (m,2H) and 5.3 (br s,1H).

For alternative preparations see (34) from (71a) and reference 17.

(470ml), and piperidine (5.7g, 6.63ml, 0.067 ml), and was refluxed under nitrogen for 1.5 hours. During this time the paraformaldehyde had dissolved to give a colourless solution. To this mixture at 25°C was added triethylphosphonoacetate (112g, 0.5mol) and the mixture heated under reflux for an additional 8 hours. The solution was cooled and concentrated under reduced pressure, benzene was added and the mixture concentrated again. After repeating this procedure, the residual oil was transferred to a 250ml flask and phosphoric acid (5ml, 85%) added. Vacuum distillation gave the pure vinylphosphonate ester 48.3g, 41% bp 90-95°C at 0.1mm Hg (lit⁸³ 98-99.3°C at 0.13 mm Hg) ¹H NMR (CCl₄) 1.35 (t,9H), 3.84-4.45 (m,6H), 6.47 (dd,1H) and 7.00 (dd,1H).

5,6,7,7a-tetrahydro-1-methyl-2-carboethoxy-3H-pyrrolizin-5-one

Sodium hydride (0.128g, 3.2 mmol, 60% dispersion in oil) was placed in a flask and washed with petrol. THF (20ml) was added followed by 5-acetylpyrrolidin-2-one (86)⁶⁵ (0.407g, 3.2 mmol). The reaction mixture was stirred for 15 mins and then ethyl-2-(diethylphosphono)acrylate⁸³ (0.708g, 3mmol) was added. The mixture was refluxed for 3 days and then partitioned between water and chloroform. The chloroform layers were dried (MgSO₄) and evaporated. Chromatography with ethyl acetate - petrol (50:50) gave a brown oil, 0.617g. IR (liquid film) 3400 (br) and 1700 ¹H NMR (CDCl₃) 1.13 - 1.56 (2t), 2.1 (m), 1.9-2.7(m) and 3.5-4.8 (m). Proton integration was not in agreement with expected product. There appeared to be two products formed - the expected product and the Michael adduct.

to a solution of clean sodium (25g, 1mol) cut into small pieces in redistilled benzyl alcohol (475g, 4.4mol) (stirring for 20 hours and warming to 70°C were required to effect complete solution) was added gradually freshly distilled ethyl chloroacetate (123g, 1.13mol) with water bath cooling. The mixture was then stirred and heated at about 80°C for 2 hours, cooled, treated with water and the oil which separated was extracted from the aqueous layer with ether. The ether extract was dried (MgSO_4), the solvent was removed, and the residue distilled under reduced pressure to obtain a mixture of ethyl and benzyl esters of benzyloxyacetic acid bp 60-180°C at 0.2mmHg (lit⁸⁴ 50-165°C at 0.3mmHg), 128g. The mixed esters were saponified by refluxing for 1.5 hours with a mixture of methanol (150ml) and potassium hydroxide (60ml, 45%). After the methanol was removed by evaporation, the residue was diluted with water and then extracted with ether to remove unchanged benzyl alcohol. Acidification of the aqueous phase released the crude benzyloxyacetic acid which was taken up in ether and purified by distillation under reduced pressure. bp 140-145°C at 0.2mmHg (lit⁸⁴ 135-140°C at 0.2mmHg) 63g, 38%.

To a solution of dicyclocarbodiimide (2.27g, 0.011 mol) in ether (20ml) at 0°C was added a solution of benzyloxyacetic acid (122)⁸⁴ (3.32g, 0.02mol) in dichloromethane (20ml) dropwise at such a rate that the temperature did not exceed 5°C. The reaction was followed by ¹H nmr, which showed that some benzyloxyacetic acid was still present (broad singlet at 10.4).

The reaction was repeated several times with an increased amount of DCC but still some acid remained.

Benzyloxyacetic methoxymethanoic anhydride (123)

To a solution of benzyloxyacetic acid (122)⁸⁴ (1.66g, 0.01mol) in ether (90ml) and triethylamine (1.11g, 1.53ml, 0.011mol) at 0°C was added dropwise a solution of methylchloroformate (1.04g, 0.85ml, 0.011 mol) in ether (50ml). The mixture was stirred overnight and the resulting triethylamine hydrochloride was filtered off and washed with ether. The combined ether filtrates were evaporated down at a high temperature to give mixed anhydride (123) 2.07g, 92% ¹H NMR (CDCl₃) 3.6 (s, 3H), 4.07 (s, 2H), 4.57 (s, 2H) and 7.3, (s, 5H). MS m/z 165 (M-COOMe), 107, 91, 79, 77 and 65.

To glutamic acid (525mg, 3.57mmol) and the mixed anhydride (123) (3.996g, 17.8mmol) and triethylamine (1.26g, 1.74ml, 12mmol) was added 4-dimethylaminopyridine (3mg, 0.029 mmol). The reaction mixture was stirred at 60°C for 8 hours and then distilled under reduced pressure. ¹HNMR showed that the mixed anhydride (123) had been recovered - 3.6 (s,3H), 4.07 (s,2H), 4.57 (s,2H) and 7.3 (s,5H).

Reaction was repeated and refluxed overnight - again (123) recovered.

Reaction repeated using DMF as a solvent - again (123) recovered.

Reaction repeated using DMF as a solvent and refluxed - again (123) recovered.

1-acetyl-5-benzyloxyacetylpyrrolidin-2-one (124) (R=Me)

(a) To N-acetylglutamic acid (Aldrich) (1.51g, 8mmol) and the mixed anhydride (123) (9.6g, 40mmol) and triethylamine (4ml, 28mmol) was added 4-dimethylaminopyridine (7.8mg, 0.064mmol). The reaction mixture was stirred at 60 - 70°C for 3 days and then water (75ml) added and the mixture extracted into chloroform. The chloroform layers were combined and washed several times with saturated sodium bicarbonate solution and dried (MgSO₄). After concentration, the reaction mixture was separated on a column using ethyl acetate as eluent. ¹HNMR of the product showed that mixed anhydride (123) had been recovered 3.6 (s,3H), 4.07 (s,2H), 4.57 (s,2H) and 7.3 (s,5H). Amount of (123) recovered 7.9g, 82%.

(7.100g, 0.19mmol) and pyridine (20ml) were heated at 110-120°C for 24 hours and then distilled under reduced pressure. Again the mixed anhydride (123) was recovered.

5-carboethoxypyrrolidin-2-one (127)

(a) Pyroglutamic acid (25g, 0.19mol), ethanol (100ml), benzene (50ml) and concentrated sulphuric acid (25g) were combined and heated at reflux for 24 hours. The reaction mixture was cooled in an ice bath and treated with 10% sodium hydroxide to pH 6. The mixture was concentrated under reduced pressure, then diluted with dichloromethane and filtered through a pad of Hyflo super cell filter aid. The filtrate was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was distilled under vacuum to give 5-carboethoxypyrrolidin-2-one (127), 8.87g, 30%.
bp 157-158°C at 2mmHg (lit⁸⁷ 159-160°C at 2mmHg)
mp 51-54°C (lit⁸⁷ 48-50°C) IR (KBr) 3230 br, 1740, 1700, 1200, 1100, 1040 ¹H NMR (CDCl_3) 1.23 (t, 3H), 2.0-2.8 (m, 4H), 3.87-4.40 (m, 3H) and 6.9 (br s, 1H).

absolute ethanol (250ml) cooled in an ice bath, was added freshly distilled thionyl chloride (30ml, 410mmol). The solution was stirred at room temperature for 1 hour and heated at reflux for 0.5 hour. The excess ethanol and hydrochloric acid were evaporated off under reduced pressure. The syrup was then diluted with absolute ethanol (200ml), the acid neutralised with potassium hydroxide in ethanol, the potassium chloride filtered off (use of Hyflo required), and the ethanol distilled off under reduced pressure. The crude diethylglutamate was heated to 140-150°C under reduced pressure for an hour or until the frothing and bubbling ceased. The desired ester (127) was then distilled through a Vigreux column 6-8cm in length at 162-165°C at 3mm Hg (lit⁸⁸ 152-153°C at 3mm Hg) giving 20g, 73% of (127) mp 48-50°C (lit⁸⁸ 48-50°C) IR (KBr) 3235 br, 1740, 1690, 1200, 1100, 1040 ¹H NMR (CDCl₃), 1.3 (t,3H), 2.3 (m,4H), 4.1 (m,3H) and 7.2 (br s,1H). (br s, 1H).

Since L-glutamic acid was used the (S)-isomer of (127) was formed.

5-Hydroxymethylpyrrolidin-2-one (128)

(a) Lithium borohydride (217mg, 10mmol) was dissolved in dry THF (20ml) and 5-carboethoxypyrrolidin-2-one (127) (1.57g, 10mmol) was added slowly in portions. The reaction mixture was stirred at room temperature for 18 hours, cooled in an ice bath and quenched by the slow addition of 20% acetic acid (30ml). The THF was evaporated off and the remaining solution was applied to a column of Dowex 50 (60ml, 1.5 x 34 cm). The column was washed with distilled water (150ml), and the combined washings were concentrated to give a yellow semisolid. The reaction was monitored by TLC which showed that the reaction had not proceeded cleanly.

sodium borohydride (5.675g, 150mmol) in t-butanol (240ml) was added methanol (48ml), over a 1 hour period. The mixture was refluxed for a further 12 hours, cooled and filtered. The reaction mixture was then concentrated under reduced pressure, extracted with chloroform, dried (MgSO_4) and concentrated to yield a solid. Chromatography using dichloromethane-methanol (10:1) gave (128), 5.32g, 77%. mp 63-65°C (lit⁸⁷ 66-68°C) IR (KBr) 3300 br and 1690 ^1H NMR (CDCl_3) 1.90-2.57 (m, 4H), 3.37-4.00 (m, 3H), 4.53 (br s, 1H) and 7.40 (br s, 1H).

5-formylpyrrolidin-2-one (119b)

(a) To a slurry of pyridinium chlorochromate (808mg, 3.75 mmol) in dichloromethane (50ml) was added a solution of the alcohol (128)⁸⁷ (288mg, 2.5mmol) in dichloromethane (20ml). The mixture was stirred for 12 hours at room temperature. TLC of the reaction mixture showed one major product had been formed along with several minor products. Chromatography using petrol initially followed by dichloromethane-methanol (10:1) gave a brown oil. T.L.C. of this brown oil showed that it now contained many products. It appeared that chromatography had in some way affected the product.

(3ml) was added dropwise to a solution of oxalyl chloride (0.5ml, 5.5mmol) in dichloromethane (10ml) at -78°C . After 5 minutes the alcohol (128) (578mg, 5mmol) in dry dichloromethane (5ml plus small amount of DMSO) was added to the clear solution. The resulting slurry was stirred vigorously for 1 hour at -78°C and allowed to warm to room temperature over 3.5 hours and then treated with triethylamine (10ml) and stirred for 1 hour. TLC at this point indicated one major plus 1 minor product. The reaction mixture was poured into water and the water layer extracted with dichloromethane. TLC of the organic phase showed many products were now present. Again it appeared that the aqueous work-up had affected the product.

Cyclopropyltriphenylphosphonium bromide (79a)

Cyclopropyltriphenylphosphonium bromide is commercially available from Aldrich or can be prepared by Schweizer's procedure⁵⁶ as follows:

In a 1-litre, three necked, round-bottomed flask equipped with a dropping funnel, sealed stirrer and an efficient reflux condenser was placed γ -butyrolactone (100g, 1.16mol) and red phosphorus (13.4g, 0.43mol). Over a half-hour interval bromine (195g, 66.5ml, 1.22mol) was added, the mixture being stirred moderately and cooled by an ice bath. The mixture was heated to 70°C and an additional 195g (66.5ml, 1.22mol) of bromine added over a half-hour interval. After the bromine addition the temperature was raised to 80°C and the mixture held at that temperature for 3 hours. Air was blown into the cooled reaction until the excess bromine and hydrogen bromide were removed. This process usually required one hour. The aerated reaction mixture was heated to 80°C and water (25ml) was added cautiously with stirring. A vigorous reaction occurred, and upon cessation of the reaction an additional 300ml of water was added. The reaction mixture of two layers and some solid residue was heated under reflux for 4 hours. Upon cooling, two layers again appeared. The product was extracted with ether (2x200ml) and dried (MgSO_4). The crude material was distilled under reduced pressure 115-118°C at 10mm Hg (lit⁹¹ 125-127°C at 13mm Hg) to give 105g, 55% of α -bromo- γ -butyrolactone. IR (liquid film) 1770 and 1160. ¹H NMR (CDCl_3) 2.2 - 3.27 (m, 2H) and 4.43 (m, 3H).

Triphenylphosphine (26.2g, 0.1mol) and bromobutyrolactone⁹¹ (16.5g, 0.1mol) were heated under reflux in dry THF for 3 hours. On cooling 16.2g (38%) of the phosphonium salt was filtered off. The crude product was dissolved in 15ml of hot methanol and reprecipitated by the addition of 70ml ethyl acetate mp 194-195°C (lit⁹² 196-197°C). IR (KBr) 1755, 1105, 750, 720 and 690 ¹H NMR (CDCl₃) 2.2-3.5 (m,2H), 4.2-5.0 (m,2H), 6.83-7.4 (m,1H) and 7.4 - 8.3 (m,15H).

Cyclopropyltriphenylphosphonium bromide (79a)

2-oxo-3-tetrahydrofuran-yl-triphenylphosphonium bromide⁹² (6.84g, 0.016mol) was pyrolyzed according to the method of Bestmann⁹³, by placing in an Abderhalden pistol and heating in vacuo at 199°C for 48 hours. The product (79a) was obtained in quantitative yields and recrystallisation of the tan-coloured solid from chloroform-ethyl acetate gave off white crystals. mp 187-190°C (lit⁵⁶ 189-190). IR (KBr) 3480, 3400, 3070, 3050, 3020, 3000 and 2960. ¹H NMR (CDCl₃) 0.4-1.0 (m,2H), 1.57-2.13 (m,2H), 3.10-3.60 (m,1H) and 7.67-8.10 (m,15H).

the fluoroborate salt of (79a) was prepared by dissolution of (79a) and excess sodium fluoroborate in aqueous methanol. Extraction of the methanolic solution with chloroform and evaporation of the dried (MgSO_4) chloroform solution gave pure cyclopropyltriphenylphosphonium tetrafluoroborate^{59b} in 93% yields.

Carboethoxycyclopropyltriphenylphosphonium tetrafluoroborate (79b)

To diisopropylamine (4.35ml, 31mmol) at 0°C in dry THF (30ml) was added n-butyllithium in hexane (1.5m, 20ml, 30mmol). The resulting solution was stirred for 15mins at 0°C, cooled to -30°C and transferred to a slurry of cyclopropyltriphenylphosphonium bromide (79a)⁵⁶ (11.50g, 30mmol) in dry THF (90ml) at -30°C. The resulting clear red solution of the ylide was stirred for 30 minutes at -30°C and transferred to a solution of ethylchloroformate (3.58g, 3.16ml, 33mmol) in dry THF (300ml). After 1 hour at -30°C, the reaction was quenched by addition of water (400ml). The mixture was extracted with chloroform (3x250ml), the chloroform extracts dried (Na_2SO_4) and concentrated to give an oily solid. The oily solid was dissolved with excess sodium fluoroborate in aqueous methanol and the methanolic solution extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and evaporated to yield a tan coloured solid, 11.12g, 80%. The crude product was recrystallised using chloroform-ether to give pure (79b), 7.51g, 54% from (79a). mp 179-181°C (lit⁵⁸ 179-181°C) IR (KBr) 3080, 3050, 3030, 3000, 2980, 2950 and 1735. ¹H NMR (CDCl_3) 0.65-1.0 (t,3H), 1.10-1.68 (m,2H), 2.00-2.38 (m,2H), 3.72-4.25 (q,2H) and 7.45 - 7.95 (m,15H).

to diisopropylamine (4.55ml, 31mmol) at 0°C in dry THF (30ml) was added n-butyllithium in hexane (1.5M, 20ml, 30mmol). The resulting solution was stirred for 15 minutes at 0°C, cooled to -30°C, and transferred to a slurry of cyclopropyltriphenylphosphonium tetrafluoroborate^{59b} (11.71g, 30mmol) in dry THF (90ml) at -30°C. The resulting clear red solution of the ylide was stirred for 30 minutes at -30°C and transferred to a solution of dimethyldisulphide (3.01g, 2.88ml, 32mmol) in dry THF (150ml). After 1 hour at -30°C, the reaction was quenched by the addition of water (400ml). The mixture was extracted with chloroform (3x250ml), the chloroform extracts dried (Na₂SO₄), filtered with the aid of Hyflo super cell and the filtrate concentrated to an oily solid. The crude product was taken up in hot chloroform and crystallised by the addition of ethyl acetate to give pure (79c) 10.88g, 83%. mp 164-166°C (lit^{59b} 166-167°C). IR(KBr) 3070, 1590, 1435, 1420, 1220, 1190 and 1060 'H NMR (CDCl₃) 1.3-2.0 (m,4H), 1.73(s,3H) and 7.50-8.0 (m,15H).

sodium hydride (220g, 5.5mmol, 60% dispersion in oil) was placed in a flask and washed with petrol. THF (25ml) was added followed by 5-acetylpyrrolidin-2-one (86)⁶⁵ (636mg, 5mmol). The mixture was stirred for 15 mins and the cyclopropylphosphonium salt (79c) (3g, 6.876mmol) was added and the mixture heated under reflux for 8 hours. The product was partitioned between water and chloroform, the chloroform layers were dried (MgSO_4) and concentrated and the product separated by chromatography using ether initially followed by ethyl acetate. The product (286 mg) was analysed by proton nmr and mass spectrometry which proved (88c) had not been formed. The analysis showed that hydrolysis of the phosphonium salt (79c) had occurred to give a mixture of Ph_3PO and 1-methylthiocyclopropyl-diphenylphosphine oxide. ^1H NMR (CDCl_3) 0.6-2.0 (m), 1.6 (s) and 7.10-8.00(m). GC/MS. More volatile species m/z 288, 273, 241, 227, 201, 185, 183 and 77. Less volatile species (Ph_3PO) m/z 277, 201/199, 185/183 and 77.

1,2,3,5,6,8a-hexahydro-7-carboethoxy-8-methyl-indolizin-5-one (88b)

This was attempted as for the methylthio derivative above, from sodium hydride (128mg, 3.2mmol), 5-acetylpyrrolidin-2-one (86)⁶⁵ (381mg, 3mmol) and cyclopropylphosphonium salt (79b) (1.156g, 2.5mmol) again it appeared that hydrolysis of phosphonium salt (79b) had occurred.

To a 20% aqueous solution of sodium hydroxide (200ml) was added cyclopropyltriphenylphosphonium bromide (79a) (7.66g, 0.02mol). The mixture was heated mildly, for 0.5 hour, then extracted with chloroform, dried (MgSO_4), concentrated and recrystallised from ethyl acetate-petrol, 4.56g, 94%. mp 130-132°C (lit⁸⁰ 132-133°C). IR(KBr), 1430, 1105, 1180, 1120, 1105, 1028, 995, and 895. ¹H NMR (CDCl_3) 0.68-1.55 (m, 5H) and 7.28-8.2 (m, 10H).

1-methylthiocyclopropyldiphenylphosphine oxide

Cyclopropyldiphenylphosphine oxide (130)⁸⁰ (1.21g, 5mmol) was dissolved in dry THF (20ml) and treated with n-butyl lithium (1.5M, 3.67ml, 5.5mmol) at room temperature. The deep red solution which developed was left stirring for 1 hour and then dimethyldisulphide (0.48g, 0.46ml, 5.15mmol) in THF (20ml) was added over 10 minutes. The solution was left stirring for 3 hours and then the solvent removed under reduced pressure. Water (50ml) was added and the mixture extracted with chloroform, the chloroform layers were dried (MgSO_4) and evaporated to give a white solid. Analysis by proton NMR indicated sulphenylation had not occurred and the starting material (130) had been recovered.

1-carboethoxycyclopropyldiphenylphosphine oxide

This was attempted as for the methylthio derivative above using cyclopropylphosphine oxide (130) (2.42g, 10mmol), n-butyl lithium (1.5M, 7.33ml, 11mmol) and methylchloroformate (973mg, 0.80ml, 10.3mmol). Again analysis showed that (130) had been recovered.

An example of the pentannulation reaction between succinimide (89) and cyclopropylphosphonium salts (79)

Sodium hydride (44mg, 1.1mmol) was placed in a flask and washed with petrol. Dry THF (5ml) was added followed by succinimide (99mg, 1mmol). The mixture was stirred at room temperature for 15 minutes and then 1-methylthiocyclopropyltriphenylphosphonium tetrafluoroborate (79c) (437mg, 1mmol) added. The reaction was refluxed for 6 hours and then the product partitioned between water - chloroform. The chloroform layer was dried (MgSO_4) and column chromatography using ethyl acetate - petrol (50/50) gave a brown oil (105mg). IR (liquid film) 3500 br, 2940, 1700, 1590 and 1430. ^1H NMR (CDCl_3) 0.67-1.77 (m), 1.90 (s), 2.67 (s), 3.13-4.17 (m) and 7.1-7.93 (m).

Reaction also attempted with DMF as solvent with temperatures less than 100°C and reaction times up to 3 days - Spectral details as above.

1,2,5,6-tetrahydro-7-carboethoxy-3H-pyrrolizin-3-one (90b)

($\text{R}=\text{CO}_2\text{Et}$)

This was attempted as for the methylthio derivative above, using sodium hydride (88mg, 2.2mmol), succinimide (198mg, 2.0mmol) and phosphonium salt (79b) (924mg, 2.0mmol). Again a brown oil was obtained (241mg). IR (liquid film) 3500br, 2940, 1700, 1590, 1430, 1350, 1300, 1260, 1240, 1210 and 1050. ^1H NMR (CDCl_3) 0.67-1.53 (m), 1.23 (t), 2.67 (s), 2.90-4.0 (m), 4.15 (q) and 7.17-8.0 (m).

Reaction also attempted with DMF as solvent with temperatures less than 100°C and reaction times up to 3 days - Spectral details as above.

suspension of sodium hydride (60% dispersion in oil; 4.32g, 0.108mol) in dry DMF (40ml). The reaction mixture was cooled to 0°C and 1,3-dibromopropane (19.88g, 0.099 mol) added. The reaction mixture was allowed to warm to room temperature and stirred for 3 days. Dilute HCl (100ml) was added and the mixture extracted with chloroform (3x50ml). The combined organic extracts were washed with dilute HCl (3x50ml), dried (MgSO₄), and the solvent removed under reduced pressure. Column chromatography with ethyl acetate-petrol (50:50) gave two products. The first to be eluted was (131), 4.38g, 22%. IR (KBr) 3420, 2980, 1950, 2940, 1700, 1670, 1440, 1400, 1240 and 1145. ¹H NMR (CDCl₃) 1.7-2.3 (m, 2H), 2.7(s, 4H), 3.1-3.9 (m, 4H). The second to be eluted was a "dimer", 1.68g, 8%. mp 194-200°C IR (KBr) 3420, 2980, 2950, 2940, 1700, 1460, 1440, 1400, 1370, 1340, 1290, 1210 and 1100. ¹H NMR (CDCl₃) 1.70-2.30 (m, 2H), 2.70 (s, 8H) and 3.49 (t, 4H).

A solution of triphenylphosphine (18.29g, 69.7mmol) and 1- (3-bromopropyl)-2,5-pyrrolidinedione (131) (14g, 63.4mmol) in chloroform (100ml) was heated under reflux for 24hrs. The mixture was cooled and filtered under suction to give the product as white crystals 28.5g, 93%. mp 130-134^oC IR (KBr) 3500, 2980, 2950, 1700, 1670, 1590 and 1430. ¹H NMR (CDCl₃) 0.55-2.3 (m,2H), 2.71 (s,4H),3.1-3.75 (m,4H) and 7.3-8.0 (m,15H).

1,2,5,6-tetrahydro-3H-pyrrolizin-3-one (133)

t-butyllithium (1.8m, 33.11ml, 59.6mmol) was added to a solution of phosphonium salt (132) (26.09g, 54mmol) in THF (50ml) and the mixture heated under reflux for 2 days. TLC showed several products had been formed. Chromatography using ethyl acetate-petrol (50/50) was not very successful and so ¹H NMR proved difficult. The main fraction collected (8.76g), however, appeared to have peaks in the ¹H NMR spectrum as (132) above.

Sodium metal (345mg, 15mmol) was dissolved in anhydrous methanol (10ml). The solution was allowed to cool and then thiophenol (1.13ml, 11mmol) was added. The solution was stirred for 15 minutes and then 3-bromopropan-1-ol (0.91ml, 10mmol) was added. The reaction mixture was stirred for 18 hours and chloroform added. The reaction mixture was filtered with the aid of Hyflo super cell and the filtrate concentrated to give an oil. Chromatography of the oil using ethyl acetate petrol (50/50) gave a pale yellow oil, 1.67g, 99%. IR (Liquid film) 3500br, 2960, 2940, 2880, 2840, 1590, 1480, 1400, 1250 and 1140 ¹H NMR (CDCl₃) 1.53-2.10 (m, 2H), 2.70 (s, 1H), 2.67-3.13 (t, 2H), 3.43-3.80 (t, 2H) and 7-7.4 (m, 5H).

1- [3-(phenylthio)propyl] -2,5-pyrrolidinedione (136)

Route (a)

Sodium metal (177mg, 7.67 mmol) was dissolved in anhydrous methanol (5ml). The solution was allowed to cool and thiophenol (0.76ml, 7.46mmol) added. The solution was stirred at room temperature for 15 minutes and then 1-(3-bromopropyl)-2,5-pyrrolidinedione (131) 1.63g, 7.38mmol) was added. The reaction mixture was stirred overnight and filtered with the aid of Hyflo super cell. The filtrate was concentrated to give (136), 975mg, 53%. mp 79-81°C. IR (KBr) 3440 br, 2930 + sh, 1770, 1760, 1695, 1570, 1475, 1435, 1410, 1335, 1250 and 1140 ¹H NMR (CDCl₃) 1.55-2.18 (m, 2H), 2.65 (s, 4H), 2.58-3.08 (t, 2H), 3.45-3.78 (t, 2H) and 7.20 (s, 5H).

to a mixture of 1-(3-phenylthio)propan-1-ol (135) (841mg, 5mmol), succinimide (496mg, 5mmol) and triphenylphosphine (1.31g, 5mmol) in dry THF (5ml) under an atmosphere of nitrogen, was added diethylazodicarboxylate (871mg, 5mmol) in dry THF (2ml) over a period of 1 hour. The resulting solution was stirred at room temperature for 3 hours and the solvent removed under reduced pressure. Chromatography using dichloromethane gave (136), 690mg, 55% as a pale yellow solid. mp 78-80°C. IR (KBr) 3440 br, 2930, 1770, 1760, 1700, 1475, 1435, 1405, 1330, 1245 and 1145. ¹H NMR (CDCl₃) 1.45-2.23 (m, 2H), 2.65 (s, 4H), 2.48-3.10 (t, 2H), 3.42-3.82 (t, 2H) and 7.22 (s, 5H).

Attempts at α -chlorination of (136) to give 1- [3-chloro-3-(phenylthio)propyl] -2,5-pyrrolidinedione

(a) To a stirred solution of phenyl sulphide (136) (997mg, 4mmol) in carbon tetrachloride (5ml) was added N-chlorosuccinimide (588mg, 4.4mmol). The solution was stirred for 6 hours and filtered. TLC of the filtrate showed that several products were present.

(b) A solution of the phenylsulphide (136) (500mg, 2mmol) in dichloromethane (5ml) was heated to reflux. A solution of sulphuryl chloride (0.1607ml, 2mmol) in dichloromethane (5ml) was added over 1.25 hours, cooled to room temperature and the solvent removed under reduced pressure. TLC again indicated that several products were present.

chromatography was inadvisable due to the reactivity of chloroalkylphenylsulphides and so attempts were made at the direct formation of phosphonium salt (134a).

3-(N-2,5-pyrrolidinedione)-1-phenylthiopropyl-1-triphenylphosphonium chloride (134a)

α -chlorination of (136) was carried out as above followed by evaporation of the solvent under reduced pressure and immediate addition of 1 equivalent of triphenylphosphine in dry THF. The solution was stirred at room temperature for 6 hours and the solvent removed under reduced pressure. The resulting product was extremely hygroscopic and isolation by ether trituration proved impossible. Isolation could also not be achieved from the formation of the tetrafluoroborate salt by dissolution of the above hygroscopic product in aqueous methanol, followed by addition of excess sodium tetrafluoroborate.

α - chlorination of 3-phenylthiopropyl-1-ol (135) to give 3-chloro-3-phenylthiopropyl-1-ol

(a) To a carbon tetrachloride (5ml) solution of 3-phenylthiopropyl-1-ol (135) (3.37g, 20mmol) at room temperature was added N-chlorosuccinimide (2.94g, 22mmol). A violent reaction occurred which quickly ceased leaving a white solid in a yellow solution. The reaction mixture was left stirring overnight in which time the reaction mixture had lightened in colour. The solid was filtered off and the solvent removed under reduced pressure to give a yellow oil. TLC indicated the presence of several products.

slowly in 10 portions over a period of 2.5 hours. Again the filtrate showed the presence of several products.

Protection of the hydroxyl group of 3-phenylthioprop-1-ol (135)

(a) as tetrahydropyranyl

3-phenylthioprop-1-ol (135) (841mg, 5mmol) and dihydropyran (0.684ml, 7.5mmol) in a solution of dry ether (10ml) containing p-toluenesulphonic acid (57.1mg, 0.3mmol), was stirred at room temperature for 3 hours. The solution was diluted with more ether and washed with saturated sodium bicarbonate solution. The ether layer was dried (MgSO_4) and evaporated under reduced pressure to give the protected alcohol, 694mg, 55%. IR (liquid film) 2960, 2940, 2880, 1590, 1485, 1405, 1255, 1135 and 1080. ^1H NMR (CDCl_3) 1.30-2.10 (m, 8H), 2.77-3.17 (t, 2H), 3.30-3.86 (m, 4H), 4.37-4.63 (m, 1H) and 6.93-7.40 (m, 5H).

(b) as α -ethoxyethyl

To a stirred solution of 3-phenylthioprop-1-ol (135) (841mg, 5mmol) in dichloromethane (10ml), was added ethylvinylether (721mg, 10mmol) and 1 drop of 2N hydrochloric acid. The solution was stirred overnight and the solvent and excess ethylvinyl ether removed under reduced pressure to give the protected alcohol, 1.18g, 98%. IR (liquid film) 3050, 2970, 2920, 2860, 1580, 1480, 1435, 1370, 1125, 1080 and 1055. ^1H NMR (CDCl_3) 1.05-1.42 (m, 6H), 1.62-2.13 (m, 2H), 2.77-3.22 (t, 2H), 3.22-3.83 (m, 4H), 4.43-4.83 (m, 1H) and 7.03-7.5 (m, 5H).

A solution of 5-phenylpentan-1-ol (135) (8.266g, 49mmol) in pyridine (10ml) was cooled to 0°C. Acetic anhydride (21ml) was added in one portion and the reaction mixture stirred at room temperature for 2.5 hours. The reaction mixture was partitioned between ether-water and the ether layer washed with 2N HCl several times. The ether layer was dried (MgSO₄) and evaporated under reduced pressure to give the protected alcohol, 10.10g, 98%. IR (liquid film) 3080, 3060, 2960 and sh, 1735, 1590, 1485, 1440, 1390, 1370, 1245, 1130 and 1040. ¹H NMR (CDCl₃) 1.63-2.16 (m, 2H), 1.97 (s, 3H), 2.70-3.07 (t, 2H), 3.87-4.23 (t, 2H) and 6.87 - 7.30 (m, 5H).

α-chlorination of hydroxyl-protected (135)

(a) tetrahydropyranyl

To a carbon tetrachloride (5ml) solution of the tetrahydropyranyl protected (135) (505mg, 2mmol) at room temperature was added N-chlorosuccinimide (267mg, 2mmol). After stirring for approximately 10 minutes the solution turned yellow. Stirring was continued overnight in which time the colour had dispersed. The reaction mixture was filtered and TLC of the filtrate showed that several products were present.

To a solution of the tetrahydropyranyl protected (135) (1.01g, 4mmol) in dry dichloromethane (5ml) at 0°C was added sulphuryl chloride (0.36ml, 4.5 mmol). The mixture was stirred for 30 minutes and the solvent evaporated at reduced pressure at room temperature. Again TLC showed the presence of several products.

α -chlorination of the α -ethoxyethyl protected (135) was carried out by the two procedures above using (i) protected alcohol (240mg, 1mmol), N-chlorosuccinimide (147mg, 1.2mmol) in carbon tetrachloride (5ml) and (ii) protected alcohol (240mg, 1mmol), sulphuryl chloride (0.201ml, 2.5mmol) in dichloromethane (5ml).

In both cases TLC again showed several products had been formed.

(c) Acetyl

To a carbon tetrachloride (10ml) solution of the acetyl protected (135) (2.10g, 10mmol) was added N-chlorosuccinimide (1.47g, 11mmol). The solution was stirred overnight and filtered. Evaporation of the solvent at reduced pressure gave 2.21g of a yellow oil. ^1H NMR (CDCl_3) 2.10 (s, 3H), 2.10-2.53 (m, 2H), 4.03-4.40 (t, 2H), 5.10-5.43 (t, 1H) and 7.0-7.6 (m, 5H). Since the proton NMR seemed promising the product was immediately reacted with triphenylphosphine (2.60g, 9.9mmol) in THF. The mixture was heated under reflux for 6 hours and the solvent removed under reduced pressure. The product could not be isolated by trituration with dry ether. Conversion to the tetrafluoroborate salt by dissolution in aqueous methanol and addition of excess sodium tetrafluoroborate also did not allow for isolation.

5 drops of hydrogen bromide in acetic acid solution was added to a solution of 4-chloro-butryl chloride (14.1g, 0.1mol) and 20% excess N-bromosuccinimide (21.36g, 0.12mol) in carbon tetrachloride (50ml). The reaction mixture was refluxed for 3 hours and filtered. Evaporation of the solvent under reduced pressure gave (137), 17.61g, 80%. IR (liquid film) 2970+sh, 1780, 1440 and 1420. ¹H NMR (CDCl₃) 2.23-2.87 (m,2H), 3.47-3.83 (t,2H) and 4.50-5.00 (t,1H).

Methyl-(2-bromo-4-chloro)butanoate(138)

α-bromo acid chloride (137) (21.99g, 0.1mol) was added dropwise over 45 minutes to absolute methanol (5ml) at 0°C. The solution was allowed to stand for 1 hour at room temperature. Ether was added and the solution washed with a small amount of sodium bicarbonate solution followed by water. The ether layer was dried (MgSO₄) and concentrated under reduced pressure to give (138), 13.14g, 61%, as an orange liquid. IR (liquid film) 2960, 1740, 1440, 1370, 1320, 1300, 1260, 1230, 1200 and 1170. ¹H NMR (CDCl₃) 2.20-2.60 (m,2H), 3.47-3.80 (t,2H), 3.70 (s,3H) and 4.27-4.60 (t,1H).

ether (10ml) was added triphenylphosphine (3.0g, 11.4mmol). The mixture was heated under reflux for 6 hours and the solvent evaporated under reduced pressure.

(b) As above except THF (10ml) used as solvent.

Both reactions were difficult to workup - trituration with dry ether did not give (139).

1-(2-bromoethyl)-2,5-pyrrolidinedione (140)

(a) To a mixture of 2-bromoethanol (12.50g, 0.1mol) and succinimide (9.91g, 0.1mol) in dry THF (50ml) under an atmosphere of nitrogen was added a solution of diethylazodicarboxylate (17.42g, 0.1mol) in dry THF (30ml) over a period of 1 hour. The resulting solution was stirred overnight and the solvent removed under reduced pressure. Chromatography using ethyl acetate was unsuccessful - separation of the product (140) from the diethylazodicarboxylate by-product was extremely difficult.

(b) Succinimide (9.91g, 0.1mol) was added cautiously to a stirred suspension of sodium hydride (60% dispersion in oil, 4.4g, 0.11mol) in dry DMF (40ml). The reaction mixture was cooled to 0°C and 1,2-dibromoethane (18.79g, 0.10mol) added. The reaction mixture was stirred at room temperature overnight and dilute HCl added. The reaction mixture was extracted with chloroform and the chloroform layers washed with dilute HCl, dried (MgSO₄) and the solvent removed under reduced pressure.

mp 55-57°C IR (KBr) 3440, 3050, 2960, 2920, 1700, 1430, 1400, 1360, 1200 and 1140. ¹H NMR (CDCl₃) 2.67 (s,4H), 3.27-3.63 (distorted t,2H) and 3.63-4.03 (distorted t,2H).

3-(N-2,5-pyrrolidinedione)-1-carbomethoxypropyl-1-triphenyl-phosphonium bromide (134b)

Halide (140) (1.03g, 5mmol) was added to a refluxing solution of methoxycarbonylmethylenetriphenylphosphorane (3.34g, 10mmol) in anhydrous ethyl acetate (10ml) and the mixture refluxed for 2 hours. The reaction mixture was washed with water, then dilute HCl followed by water. The ethyl acetate layer was concentrated under reduced pressure ¹H NMR (CDCl₃) showed that the phosphorane starting material had been recovered.

Reaction repeated using DMF as solvent with a reaction time of 4 hours at a temperature of 100°C. Partition between water/chloroform and work-up as above gave recovery of the starting phosphorane.

3-hydroxypropyltriphenylphosphonium chloride (143)

Triphenylphosphine (55.08g, 0.21mol) was dissolved in dry ether (200ml) and 1-chloro-3-hydroxypropane (28.36g), 0.3mol) added. The clear solution immediately darkened. The resulting solution was heated under reflux for 36 hours and a white solid was deposited on cooling. The solvent was removed under reduced pressure to give 64.84g, 87% of (143) which was recrystallised from chloroform-ethyl acetate.

2850, 1580, 1480, 1430, 1200, 1140, 1120, 1100, 1050, 990, 890, and 870 ¹H NMR (CDCl₃) 1.50-2.23 (m, 2H) 3.33-4.10 (m, 4H), 3.90(s, 1H) and 7.23-7.87 (m, 15H). Microanalysis found; C, 69.96; H, 6.24; C₂₁H₂₂OPCl requires; C, 70.68; H, 6.21.

3-hydroxypropyldiphenylphosphine oxide (144)

Phosphonium salt (143) (26g, 70mmol) was dissolved in methanol (100ml) and sodium hydroxide (6g, 0.15mol in 50ml water) added. The solution was stirred with gentle heating overnight and the reaction mixture extracted into chloroform-water. The chloroform layers were dried (MgSO₄) and concentrated under reduced pressure to give a white solid (trituration with ether maybe necessary) 17.86g 98%. Recrystallisation from ethyl acetate gives pure (144) mp 100-102°C. IR (KBr) 3320br, 3020, 2915, 2900, 2850, 1580, 1480, 1430, 1160, 1110, 1050 and 900. ¹H NMR (CDCl₃) 1.53-2.70 (m, 4H), 3.43-3.77 (t, 2H), 3.93 (s, 1H) and 7.0-8.0 (m, 10H). Microanalysis found; C, 68.90; H, 6.69; C₁₅H₁₇O₂P requires C, 69.22; H, 6.58.

3-hydroxy-1-methylthiopropyldiphenylphosphine oxide (145a)

Phosphine oxide (144) (6.51g, 25mmol) in dry THF (100ml) and tetramethylethylenediamine (4.13ml, 27.5mmol) was treated with n-butyllithium (1.54M, 35.7ml, 55mmol) at -78°C. After 15 minutes the orange anion was added to a solution of dimethyl disulphide (2.32ml, 25.75 mmol) in dry THF (50ml) at -78°C and the resulting solution stirred for 30 minutes. Aqueous sodium carbonate was added and the product extracted several times with chloroform.

sodium chloride, dried (MgSO_4) and evaporated under reduced pressure. Chromatography using ethyl acetate gave pure (145a) as a white solid on trituration with ether, 6.92g, 90% mp 157-159°C. IR (KBr) 3350br, 3080, 3060, 2960, 2920, 2900, 2860, 1590, 1485, 1435, 1315, 1160, 1120, 1070, 1050, 880 and 800. ^1H NMR (CDCl_3) 1.53-2.40 (m, 2H), 1.92 (s, 3H), 3.17-3.63 (m, 1H+1H), 3.63-3.90 (t, 2H) and 7.10-8.0 (m, 10H). Microanalysis found; C, 62.49; H, 6.29; $\text{C}_{16}\text{H}_{19}\text{O}_2\text{SP}$ requires; C, 62.72; H, 6.25.

3-hydroxy-1-phenylthiopropyldiphenylphosphine oxide (145b)

This was prepared as for the methylthio derivative (145a) above using phosphine oxide (144) (6.76g, 26mmol), TMEDA (4.30ml, 28.6mmol) n-butyllithium (1.54m, 37.14ml, 57.2mmol) and diphenyldisulphide (5.85g, 26.78 mmol) but using an acidic work-up with dilute HCl. Chromatography using ethyl acetate gave pure (145b) as a white solid on trituration with ether 3.93g, 41%. mp 116-118°C. IR (KBr) 3300br, 3070, 3050, 3020, 2950, 2920, 2860, 1590, 1485, 1440, 1320, 1180, 1120, 1060, 1050, 910 and 850. ^1H NMR (CDCl_3) 1.83-2.50 (m, 2H) 3.27 (br s, 1H), 3.67-4.17 (t+m, 2H+1H), 7.0 (s, 5H) and 7.10-8.00 (m, 10H). Microanalysis found; C, 68.02; H, 5.78; $\text{C}_{21}\text{H}_{21}\text{O}_2\text{SP}$ requires C, 68.46; H, 5.74.

To a mixture of alcohol (145a) (3.06g, 10mmol), succinimide (1.02g, 10.3mmol) and triphenylphosphine (2.70g, 10.3mmol) in dry THF (25ml) under nitrogen was added a solution of diethylazodicarboxylate (1.794g, 10.3mmol) in dry THF (5ml) over a period of 1 hour. The resulting solution was stirred at room temperature for 48 hours and the solvent removed under reduced pressure. Chromatography using ether initially followed by ethyl acetate gave (142a), 1.76g, 45% as a white solid. mp 182-184°C. IR (KBr) 3500, 3060, 3020, 2980, 2960, 2900 + sh, 1700, 1590, 1490, 1440, 1400, 1370 and 1340. ¹H NMR (CDCl₃) 1.73-2.30 (m, 2H), 2.0 (s, 3H), 2.60 (s, 4H), 2.82-3.40 (m, 1H), 3.40-4.0 (t, 2H) and 7.0-8.0 (m, 10H). Microanalysis found (best of several attempts); C, 59.41; H, 5.61; N, 3.77; C₂₀H₂₂O₃NPS requires; C, 62.00; H, 5.72; N, 3.61.

3-(N-2,5-pyrrolidinedione)-1-phenylthiopropyl-1-diphenylphosphine oxide (142b)

This was prepared as for the methylthio derivative (142a) above using alcohol (145b) (3.58g, 9.7mmol), succinimide (0.9909g, 10mmol), triphenylphosphine (2.62g, 10mmol) and diethylazodicarboxylate (1.74g, 10mmol). Chromatography using ether initially followed by ethyl acetate gave (142b), 3.78g, 87% as a white solid. mp 188-192°C. IR (KBr) 3450, 3050, 3020, 2990, 2940, 2910, 1700, 1590, 1480, 1440, 1400, 1370 and 1345. ¹H NMR (CDCl₃) 1.70-2.37 (m, 2H), 2.51 (s, 4H), 3.20-4.00 (m+t, 1H+2H), 7.0 (s, 5H) and 7.20-8.00 (m, 10H). Microanalysis found; C, 66.43; H, 5.35; N, 3.22; C₂₅H₂₄NO₃SP requires C, 66.80; H, 5.38; N, 3.11.

example of the pentannulation reaction of phosphine oxide (142).

To diisopropylamine (0.14ml, 1.033mmol) at 0°C in THF (1ml) was added n-butyllithium (1.54M, 0.65ml, 1mmol). The resulting solution was stirred for 15 minutes at 0°C, cooled to -78°C and transferred to a slurry of the phosphine oxide (142b)(450mg, 1mmol) in THF (3ml) at -78°C. The reaction mixture was stirred overnight at room temperature and ammonium chloride solution added. The mixture was extracted into chloroform and the chloroform layers dried (MgSO₄) and evaporated at reduced pressure. Chromatography using ethyl acetate did not yield the expected product. ¹H NMR contained peaks typical of a phosphine oxide.

The above reaction was repeated and included a 24 hour reflux, but the proton NMR showed that a phosphine oxide was still present.

Attempts at the reaction using n-butyllithium as the base, both at room temperature and reflux, still gave a proton nmr spectrum that contained peaks due to phosphine oxide.

diphenyl disulphide (54.0g, 0.25mol) was dissolved in dichloromethane (11) in a 3 litre round-bottomed flask equipped with stirrer, addition funnel and nitrogen line. The solution was cooled to 5°C, and briefly swept with nitrogen. Bromine (40g, 0.25mol) in dichloromethane (50ml) was added over a few minutes and the solution stirred at 5-10°C for 30 minutes.

Z-1,4-dichlorobut-2-ene (65.0g, 0.5mol) was then added rapidly. The red solution was allowed to warm to room temperature and stirred for a total of 8-12 hours. The solvent was removed under reduced pressure and the crude yield was nearly quantitative.

Chromatography using ethyl acetate-petrol (50/50) gave pure (147) 152.7g, 97.3% as a colourless oil. ¹H NMR (CDCl₃) 3.75 (ddd, 1H), 3.84 (dd, 1H), 3.93 (t, 1H), 4.09 (dd, 1H), 4.40 (t, 1H) 4.81 (ddd, 1H), 7.45 (m, 3H) and 7.6 (m, 2H).

erythro-1,4-dichloro-2-bromo-3-phenylthiobutane (150)

Prepared as (147) above using E,-1,4-dichlorobut-2-ene (65g, 0.5mol) in place of the Z-isomer to give 48.2g, 76% as a white semi-solid ¹H NMR (CDCl₃) 3.79 (dt, 1H), 3.97 (d, 2H), 4.12 (dd, 1H), 4.25 (dd, 1H), 4.55 (dt, 1H), and 7.3-7.6(m, 5H).

(147) (131g, 0.417mol) was dissolved in dry ether (1.3l) in a 2 litre flask equipped with a good overhead stirrer, low temperature thermometer, and nitrogen line. The system was flushed with nitrogen and cooled to -55°C . DBU (66.0g, 0.434mol) was added dropwise with good stirring. After about 1 hour the solution was allowed to warm slowly to room temperature with good stirring. After about 8 hours the reaction was thick with precipitated DBU-HBr. The mixture was filtered, and the filter-cake washed well with ether (500ml). The ether solution was washed with water (500ml), 5% hydrochloric acid (250ml) and saturated sodium chloride solution (250ml) and dried (MgSO_4). The ether was evaporated under reduced pressure to give (148), 95g, 83% of a dark purple oil. (Some unreacted (147) present). $^1\text{H NMR}$ (CDCl_3) 3.98 (br s, 2H), 4.35 (d, 2H), 6.41 (tt, 1H) and 7.3 (m, 5H).

Z-1,4-dichloro-2-phenylthiobut-2-ene (151)

Prepared as (148) above except (150) (131g, 0.417mol) used in place of (147) to give 95g (crude) of (151) (approximately 15-20% unreacted (150) present) $^1\text{H NMR}$ (CDCl_3) 3.98 (brs, 2H), 4.35 (d, 2H), 5.82 (t, 1H) and 7.3 (m, 5H).

Crude E-(148) or Z-(151) (9.5g, 36.7mmol, 90% pure) was dissolved in dry DMF (100ml) and triphenylphosphine (21.1g, 80.7mmol) added. The reaction flask was flushed with nitrogen and stirred at room temperature for 3 days. The mixture, containing a purple precipitate, was added to dry acetone (200ml) and stored in a freezer overnight. The solid was filtered off and dissolved in a small amount of dichloromethane, treated with activated charcoal and diluted with 2-3 volumes of dry acetone. After crystallisation in the freezer, the nearly white (84) was filtered off and dried at 55°C at 1mm Hg. A second crop was obtained by mixing the filtrates adding ether and recrystallising the precipitate. (84) was obtained as white crystals, 17g, 61% total yield. mp 162-166°C (lit 164-166°C) ¹H NMR (CDCl₃) 5.09 (br d, 2H), 5.19 (ddd, 2H), 6.37 (ddd, 1H), 6.57 (m, 2H), 7.16 (m, 3H), 7.7 (m, 24H) and 7.9 (m, 6H).

Example of the attempted cyclisation reaction between succinimide and butadienylphosphonium salt (84)

Succinimide (99mg, 1mmol) and potassium carbonate (401mg, 2.9mmol) in dry DMF (2ml) was stirred at room temperature for 30 minutes. A solution of phosphonium salt (84) (757mg, 1mmol) was added slowly over 3-5 hours and the solution stirred for 24 hours at room temperature. TLC showed that several products had been formed in the reaction. Chromatography using ethyl acetate-petrol (50/50) proved difficult and analysis by proton NMR showed that the expected product (91) had not been formed.

to be (91).

The reaction was repeated using THF as the solvent and heated under reflux for 48 hours again TLC showed several products had been formed, none of which appeared to be (91).

The reaction was repeated replacing the potassium carbonate with sodium hydride and still the same results were obtained.

- Naturst., 1982 41, 115 and references cited therein.
- (b) D.J. Robins, Adv. Heterocycl. Chem., 1979, 24, 247.
 - (c) A. Klasek and O. Weinbergova, Recent Dev. Chem. Nat. Carbon Compd., 1975, 6, 35.
 - (d) F.L. Warren, Alkaloids (N.Y.) 1970, 12, 245.
 - (e) C.K. Atal, Lloydia, 1978, 41, 312.
2. (a) L.B. Bull, C.C.J. Culvenor and A.T. Dick, "The Pyrrolizidine Alkaloids", North Holland Publishing Co. Amsterdam 1968.
- (b) M.M. Ames and J.S. Kovach, Cancer Res., 1979, 39, 3564.
 - (c) J.S. Kovach, M.M. Ames, G. Powis, C.G. Moertel, R.G. Hahn and E.T. Creagen, Cancer Res., 1979, 39, 4540.
3. A.R. Mattocks "Phytochemical Ecology", ed. J.B. Harborne, Academic Press, London and New York, 1972, p179.
4. A.R. Mattocks, Toxicol. Lett., 1982, 14, 111.
5. A.R. Mattocks "Chemistry and Toxicology of Pyrrolizidine Alkaloids", Academic Press, London and New York, 1986.
6. N.K. Kochetkov and A.M. Likhoshesterov, Adv. Heterocycl. Chem., 1965, 5, 315.
7. J.W. Barrett and R.P. Linstead, J. Chem. Soc., 1936, 611.
8. C.C.J. Culvenor, M.L. Heffernan and W.G. Woods, Aust. J. Chem., 1965, 18, 1605.
9. R. Robinson, "The Structural Relations of Natural Products", p.72. Oxford Univ. Press (Clarendon), London and New York 1955.

11. (a) E.K. Kunec and D.J. Robins, J. Chem. Soc., Perkin Trans.
1, 1987, 1089.
- (b) R.B. Herbert, Nat. Prod. Rep., 1985, 2, 163.
12. D.J. Robins, J. Chem. Soc., Chem. Commun., 1982, 1289.
13. D.J. Hart and T-K Yang, Tetrahedron Lett., 1982, 23, 2761.
14. D.J. Hart and T-K Yang, J. Chem. Soc., Chem. Commun.,
1983, 135.
15. A.R. Chamberlin and J.Y.L. Chung, J. Am. Chem. Soc.,
1983, 105, 3653.
16. T.L. Macdonald and B.A. Narayanan, J. Org. Chem., 1983,
48, 1129.
17. D.A. Burnett, J-K Choi, D.J. Hart and Y-M Tsai, J. Am.
Chem. Soc., 1984, 106, 8201.
18. "The Alkaloids", ed. M.F. Grundon (Specialist Periodical
Reports) The Royal Society of Chemistry, London. Vol. 1
onwards.
19. R.F. Manske, Alkaloids, Vol. 14, Ch. 8.
20. L.E. Overman and K.L. Bell, J. Am. Chem. Soc., 1981, 103,
1851.
21. S.R. Johns, J.A. Lamberton, A.A. Sioumis and R.I. Willing,
Aust. J. Chem., 1969, 22, 775.
22. S.R. Johns, J.A. Lamberton and A.A. Sioumis, Aust. J.
Chem., 1969, 22, 793.
23. S.R. Johns, J.A. Lamberton and A.A. Sioumis, Aust. J.
Chem., 1969, 22, 801.
24. S.R. Johns, J.A. Lamberton, A.A. Sioumis, H. Soares and
R.I. Willing, Aust. J. Chem. 1971, 24, 1679.
25. N.K. Hart, S.R. Johns and J.A. Lamberton, Aust. J. Chem.,
1972, 25, 817.

28. T. Shono, Y. Matsumura, K. Uchido, K. Tsubata and A. Makino, J. Org. Chem., 1984, 49, 300.
29. B.P. Wijnberg and W.N. Speckamp, Tetrahedron Lett., 1981, 22, 5079.
30. N.A. Khatri, H.F. Schmitthenner, J. Shringarpure and S.M. Weinreb, J. Am. Chem. Soc., 1981, 103, 6387.
31. A.R. Chamberlin, H. Nguyen and J.Y.L. Chung, J. Org. Chem., 1984, 49, 1682.
32. J.W. Daly, Fortschr. Chem. Org. Naturst., 1982, 41, 205.
33. J.W. Daly, T. Tokuyama, T. Fujiwara, R.J. Highet and I.L. Karle, J. Am. Chem. Soc., 1980, 102, 830.
34. K.B. Becker, Tetrahedron, 1980, 36, 1717 and references cited therein.
35. G. Wittig and U. Schollkopf, Chem. Ber., 1954, 87, 1318.
36. I. Gosney in "Organophosphorus reagents in Organic Synthesis" ed. J.I.G. Cadogan, Academic Press, London and New York, 1979, p18.
37. L. Horner, H.Hoffmann, and H.G. Wippel, Chem. Ber., 1958, 91, 61.
38. A.E. Arbusov and A.A. Dunin, Ber. Deut. Chem. Ges., 1927, 60, 291.
A.E. Arbusov and A.I. Razumov, J. Russ. Phys. Chem. Soc., 1929, 61, 623
39. L. Horner, H. Hoffmann, H.G. Wippel, and G. Klahre, Chem. Ber., 1959, 92, 2499.
H. Hoffmann, Angew. Chem., 1959, 71, 379.
40. B.J. Walker in "Organophosphorus reagents in Organic Synthesis" ed. J.I.G. Cadogan, Academic Press, London and New York, 1979, p157.

42. G.H. Posner and S-B.Lu, J. Am. Chem. Soc., 1985, 107, 1424.
43. J.M. McIntosh and H.B.Goodbrand, Synthesis, 1974, 862.
44. J.M. McIntosh and R.S. Steevensz, Can. J. Chem., 1977, 55, 2442.
45. A.T. Hewson, Tetrahedron Lett., 1978, 3267.
46. A.G. Cameron and A.T. Hewson, J. Chem. Soc., Perkin Trans. 1., 1983, 2979.
47. J.P. Marino and E. Laborde, J. Am. Chem. Soc., 1985, 107, 735.
48. A.G. Cameron, A.T. Hewson and M.I. Osamor, Tetrahedron Lett., 1984, 2267.
49. A.G. Cameron, A.T. Hewson and A.H. Wadsworth Tetrahedron Lett., 1982, 561.
50. A.T. Hewson and D.T. McPherson, Tetrahedron Lett., 1983, 24, 5807.
51. A.T. Hewson and D.T. McPherson, J. Chem. Soc., Perkin Trans. 1., 1985, 2625.
52. A.T. Hewson and D.T. McPherson, Tetrahedron Lett., 1983, 647.
53. S.K. Richardson, PhD Thesis, Sheffield City Polytechnic, 1985.
54. M. Mikolajczyk, S. Grzejszczak and K. Korbacz, Tetrahedron Lett., 1981, 3097.
55. (a) S. Warren and A.T. Zaslona, Tetrahedron Lett., 1982, 4167.
- (b) J.I. Grayson, S. Warren and A.T. Zaslona, J. Chem. Soc., Perkin Trans.1., 1987, 967.

57. E.E. Schweizer, T. Minami, and D.M. Crouse, J. Org. Chem., 1971, 36, 4028.
58. P.L. Fuchs, J. Am. Chem. Soc., 1974, 96, 1607.
59. (a) J.P. Marino and R.C. Landick, Tetrahedron Lett., 1975, 4531.
- (b) J.P. Marino and M.P. Ferro, J. Org. Chem., 1981, 46, 1828.
60. P.L. Fuchs, Tetrahedron Lett., 1974, 4055.
61. G. Buchi and M. Pawlak, J. Org. Chem., 1975, 40, 100.
62. S.F. Martin and S.R. Desai, J. Org. Chem., 1978, 43, 4673
63. R.J. Pariza and P.L. Fuchs, J. Org. Chem., 1983, 48, 2306
- R.J. Pariza and P.L. Fuchs, J. Org. Chem., 1985, 50, 4252.
64. W. Flitsch and S.R. Schindler, Synthesis, 1975, 685.
65. M.J. Fray, E.J. Thomas and J.D. Wallis, J. Chem. Soc., Perkin Trans. 1., 1983, 395.
66. (a) H.D. Dakin and R. West., J. Biol. Chem., 1928, 78, 745.
- (b) H.D. Dakin and R. West., J. Biol. Chem., 1928, 78, 91.
67. J.A. King and F.H. McMillan, J. Am. Chem. Soc., 1952, 74, 2859.
68. J.W. Cornforth and D.F. Elliot, Science, 1950, 112, 534.
69. G. Singh and S. Singh, Tetrahedron Lett., 1964, 3789.
70. (a) R. Huisgen, H. Gotthardt, H.O. Bayer and F.C. Schaefer, Angew. Chem. Int. Ed. Engl., 1964, 3, 136.
- (b) R. Huisgen, H. Gotthardt and H.O. Bayer, Tetrahedron Lett. 1964, 481, Angew. Chem. Int. Ed. Engl., 1964, 3, 135.
- (c) I.J. Turchi and M.J.S. Dewar, Chem. Rev., 1975, 389 and references cited therein.

- (b) J.A. King and F.H. McMillan, J. Am. Chem. Soc., 1951, 73, 4911.
72. J.A. King and F.H. McMillan, J. Am. Chem. Soc., 1955, 77, 2814.
73. (a) R.H. Wiley and O.H. Borum, J. Am. Chem. Soc., 1950, 72, 1626.
- (b) R.H. Wiley, Science, 1951, 114, 448
74. P.A. Levene and R.E. Steiger, J. Biol. Chem., 1927, 74, 689; 1928, 79, 95.
75. N.L. Allinger, G.L. Wang and B.B. Dewhurst, J. Org. Chem., 1974, 39, 1730 and references cited therein.
76. (a) W. Steglich and G. Hofle, Ang. Chem. Int. Ed. Engl., 1969, 8, 981.
- (b) G. Hofle, W. Steglich and H. Vorbruggen, Ang. Chem. Int. Ed. Eng. 1978, 17, 569.
- (c) J. Lepschy, G. Hofle, L. Wilschowitz and W. Steglich, Liebigs Ann. Chem., 1974, 1753.
77. (a) E.E. Schweizer and K.K. Light, J. Am. Chem. Soc., 1964, 86, 2963.
- (b) E.E. Schweizer and K.K. Light, J. Org. Chem. 1966, 31, 870.
- (c) E.E. Schweizer, J. Am. Chem. Soc., 1964, 86, 2744.
78. J.G. Bottaro, Syn. Commun. 1985, 15, 195.
79. G.B. Spero, A.V. McIntosh, Jr. and R. H. Levin, J. Am. Chem. Soc., 1948, 70, 1907
80. P.F. Cann, D. Howells and S. Warren J. Chem. Soc., Perkin Trans.1., 1972, 304.
81. B.M. Trost and R.A. Kunz, J. Org. Chem., 1974, 39, 2648.

83. M.F. Semmelhack, J.C. Tomesch, M. Czarny and S. Boettger, J. Org. Chem., 1978, 43, 1259.
84. F. Benington and R.D. Morin, J. Org. Chem., 1961, 26, 194.
85. G.H. Cleland and F.S. Bennett, Synthesis, 1985, 681.
86. J.S. McMurray and D.F. Dyckes, J. Org. Chem., 1985, 50, 1112.
87. M.E. Condon, E.W. Petrillo, Jr., D.E. Ryono, J.A. Reid, R. Neubeck, M. Puar, J.E. Heikes, E.F. Sabo, K.A. Losee, D.W. Cushman and M.A. Ondetti, J. Med. Chem., 1982 25 250. J. Med. Chem., 1982, 25, 250.
88. R.B. Silverman and M.A. Levy, J. Org. Chem., 1980, 45, 815.
89. K. Soai, H. Oyamada, and A. Oookawa, Syn Commun., 1982, 12, 463.
90. G. Bollinger and J.M. Muchowski, Tetrahedron Lett., 1975 2931.
J.W. Bruin, H. de Koning and H.O. Huisman, Tetrahedron Lett., 1975, 4599.
91. Org. Syn. Coll. Vol. 5. page 255.
92. S. Fliszar, R.F. Hudson and G. Salvadori, Helv. Chim. Acta., 1963, 46, 1580.
93. H.J. Bestmann, H. Hartung and I. Pils, Angew. Chem. Int. Ed. Eng., 1965, 4, 957.
94. M.D. Crenshaw and H. Zimmer, J. Het. Chem., 1984, 623.
95. O. Mitsunobu, M. Wada, and T. Sano, J. Am. Chem. Soc., 1972, 94, 679.
96. J.G. Gleason and D.N. Harpp, Tetrahedron Lett., 1970, 3431.
D.N. Harpp, L.Q. Bao, C.J. Black, R.A. Smith and J.G. Gleason, Tetrahedron Lett., 1974, 3235.

98. W. Flitsch and K. Pandl, Liebigs Ann. Chem., 1987, 649.
99. W. Flitsch and P. Russkamp, Liebigs Ann. Chem., 1983, 521.

As part of this project the author has attended the following lecture courses at Sheffield University:

Functional group interconversions.

Some aspects of radical chemistry.

The anomeric effect and all that.

Stereodifferentiating reactions.

Natural product synthesis.

The author has attended research colloquia given by internal and external speakers at Sheffield City Polytechnic and Sheffield University.

The author has also attended symposia on:

Stereochemistry (Sheffield 1986)

Organic chemistry (Nottingham 1985, 1986, 1987 and London 1985, 1986).